

# **PROCEEDINGS**

**Board of Scientific Counselors**

**Bethesda Marriott  
Pooks Hill  
Bethesda, Maryland**

**January 27 and 28, 1983**

**National Cancer Institute  
Division of Cancer Treatment  
Bethesda, Maryland**

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## ATTENDEES

BSC Meeting January 27-28, 1983

### DCT Board Members

Dr. Dani Bolognesi  
Dr. David Bragg  
Dr. Paul Calabresi  
Dr. Max Cooper  
Dr. Philip DiSaia  
Dr. Gertrude Elion  
Dr. M. M. Elkind  
Dr. James Goldie  
Dr. Leon Goodman  
Dr. Samuel Hellman  
Dr. Susan Horwitz  
Dr. Brigid Leventhal  
Dr. Paul Marks  
Dr. Theodore Phillips  
Dr. Carol Portlock  
Dr. Efraim Racker  
Dr. Samuel Wells, Jr.

### NCAB Member

Dr. Tim Lee Carter

### Visitors

Mr. Fred Avis  
Sikha Bhar  
Mrs. William Blair, Jr.  
K. Boching  
Dr. Arthur Bogden  
Mr. Jerry Boyd  
Mr. Ray Bramhall  
Ms. Barbara Consolazio  
Ms. Cheryl Dozier  
Ms. Elizabeth Elsberg  
Ms. Rebecca Heckard  
Dr. John Johnson  
M. Kastello  
R. Kouri  
Dr. Deloros Kucha

### Invited Guests

Dr. Neal Castagnoli, Jr.  
Dr. Charles Coltman  
Dr. William Donegan  
Dr. John Durant  
Dr. Alvan Feinstein  
Dr. Emil Freireich  
Dr. E. Carmack Holmes  
Prof. Fernand Labrie  
Dr. Charles Moertel  
Dr. Robert Wittes

### NCI-NIH Staff

Dr. Amelia Acierto  
Dr. Matti Al-Aish  
Ms. Mary Ann Anerino  
Mr. Mike Bacon  
Dr. Samuel Broder  
Ms. Ann Carpenter  
Dr. Bruce Chabner  
Mr. Don Christoferson  
Mr. Damian Crane  
Mr. J. Paul Davignon  
Dr. Vincent T. DeVita  
Divya Dhokai  
Ms. Angelia Douglas  
Dr. John Driscoll  
Mr. James Doyle  
Dr. Mario Eisenberger  
Dr. Susan Ellenberger  
Ms. Regina Ewig  
Ms. Naomi FitzGibbon  
Mr. Clarence Fortner  
Dr. Abraham Goldin  
Mr. Michael Goldrich  
Dr. Luz Hammershaimb  
Dr. Harry Handelsman  
Ms. Kim Horgan  
Dr. Daniel Hoth  
Ms. Susan Hubard  
Dr. Edwin Jacobs

Visitors (continued)

Dr. John Landon  
Ms. Mary Lasker  
Mr. Herman Liljs  
Mrs. Shirley Marty  
Dr. Jim McCoy  
G. C. McMelton  
Dr. Mike Radtke  
Ms. Shirley Ragland  
Ms. Ann Marie Sekman  
Dr. William Shingelton  
Dr. Bernard Sloan  
Dr. Howard Walker  
Dr. W. Woods

NCI-NIH Staff (continued)

Dr. David Jofte  
Mr. Gary Kelley  
Dr. Jack Killen  
Mr. Mark Kochevar  
Dr. F. J. Mahoney  
Dr. R. Makuch  
Dr. Tony Mead  
Dr. Nabeeb Mourad  
Dr. James Murray  
Dr. M. V. Nadkarni  
Dr. Ven Narayanan  
Ms. Eleanor Nealon  
Mr. Bill New  
Ms. Emily Olausen  
Dr. Robert Oldham  
Dr. Ken Paull  
Dr. Philip Perkins  
Dr. David Pistenmaa  
Dr. Juan Posada  
Mr. Roger Powell  
Dr. Kendall Powers  
Dr. Frank Quinn  
Ms. Ann Rafayco  
Dr. Elizabeth Read  
Ms. Helene Rodriquez  
Mr. T. R. Rogers  
Ms. Kathy Russell  
Dr. Saul Schepartz  
Ms. Julie Sen  
Dr. Robert Shoemaker  
Dr. Richard Simon  
Dr. Alfred Smith  
Dr. Matt Suffness  
Ms. Virginia Suppers  
Mrs. Cathy Thomas  
Ms. Dorothy Tisevich  
Ms. Zaiga Tums  
Dr. Richard Ungerleider  
Dr. John Venditti  
Mr. Jim Vennetti  
Dr. Mary Wolpert

BOARD OF SCIENTIFIC COUNSELORS  
DIVISION OF CANCER TREATMENT

Day 1 - January 27, 1983

I. CHAIRMAN'S REMARKS - DR. SAMUEL HELLMAN

Dr. Hellman convened the meeting and welcomed the members of the Board of Scientific Counselors (BSC or Board), their guests, and especially members of the Surgical Oncology Research Development subcommittee (SORDS). He drew attention to the conflict-of-interest guidelines for the meeting and then reported on two meetings attended by Division of Cancer Treatment (DCT) representatives.

Dr. Hellman reported that he and Dr. Bruce Chabner represented the DCT at the November 29, 1982 meeting of the National Cancer Advisory Board (NCAB). At this meeting, Dr. Hellman presented the BSC's view that POIs should continue to be a major funding mechanism to support the development of new cancer treatments.

Dr. Hellman also reported that he, Dr. Bolognesi and Dr. Marks, members of DCT's Budget Subcommittee, recently met to review the 1983 budget materials and to discuss the Board's concern over the review process for POIs. They were assured that the NCAB subcommittee on the review of POI grants, headed by Dr. Maureen Henderson, was studying how to weight subprojects within POI grant proposals. They were also informed that this NCAB subcommittee had broad representation from the scientific community and was sympathetic to the Board's concerns. The problem of maintaining a reasonable number of grants with reduced funds was also discussed at the DCT Budget subcommittee meeting. If budget cuts were

severe, it was suggested that the DCT Director, Dr. Chabner, could reduce the funding of P01 grant proposals with priority scores in a discretionary "swing" range.

The Board had no questions or comments on the Chairman's remarks. Dr. Hellman then introduced Dr. DeVita, Director of the National Cancer Institute (NCI).

## II. NCI DIRECTOR'S REPORT - DR. VINCENT T. DEVITA

### FY 1983 NCI BUDGET

Dr. DeVita began his presentation by discussing the FY 1983 NCI budget. He reported that Congress had passed a continuing resolution for \$983 million, a \$28 million increase over the \$955 million allocated in the President's FY 1983 budget and a \$40 million increase over the FY 1982 appropriation. Dr. DeVita then summarized how the \$28 million increase over the President's Budget would be allocated.

Dr. DeVita reported that \$15 million of the \$28 million had been earmarked for restoration of indirect costs in the research grants pool. He indicated that the remaining \$13 million would be used to increase the number of research grants funded in FY 1983 and to modify the funding plan for grant awards.

Dr. DeVita stated that overall funding for R01 and P01 projects will actually increase by about \$26.8 million. The Centers Program and Research Career Awards will increase by approximately \$2 million and \$0.5 million, respectively. Other increases include \$2.7 million for the Cooperative Group Program (this increase will cover the estimated cost of the organ systems transfer to DCT), \$2.9 million for the National Research Services

Awards, \$2 million for the Intramural Research Program and \$1.7 million for the Organ Systems Program. Dr. DeVita explained that these increases add up to more than the \$28 million increase over the President's Budget. The difference, almost \$15 million, was taken from the contract line, decreasing it from about \$145 to \$129 million. The net increase in the research grant pool amounts to about \$40 million.

Dr. DeVita commented that he could not discuss the FY 1984 budget since it had not been presented to Congress. He stated, however, that although the NCI was expected to be included in the anticipated freeze on domestic spending, he believed that the NCI will be able to cover its requirements for 1984. In the meantime, the NCI is proceeding to plan for initiating its high priority programs in FY 1984.

#### P01 PROGRAM PROJECT GRANTS

Dr. DeVita stated that he would like to dispel rumors that the NCI believes that P01 grants are less valuable than individual R01 grants. He remarked that this debate ensues every year because of the continuing struggle to reach the 5,000 research grant level. In support of the P01 grant mechanism, Dr. DeVita indicated that it is a valuable instrument for supporting an integrated program of clinical and basic research. He noted that the average cost of each project within a P01 grant is approximately equal in cost to an individual R01 grant.

Dr. DeVita also stated that the current procedures for scoring P01 grant applications have not been changed. Only when the NCAB subcommittee, chaired by Dr. Henderson, develops a weighted scoring system will the scoring of P01 grants be modified. He stated that the subcommittee was

currently dealing with the issue of determining relatedness among projects and incorporating this concept into the scoring system. Dr. DeVita indicated that the planned modifications made in the P01 grant review system could strengthen the P01 grant as a NCI funding mechanism.

Dr. DeVita emphasized that the bottom line for all programs supported at the National Institutes of Health (NIH) is the quality of the research project. He explained that the Science Citation Index study currently underway will attempt to identify which grant instruments have given rise to major scientific discoveries. He predicted that no single funding instrument will dominate and that a number of discoveries will have been made under more than one granting mechanism. If so, this will illustrate the need for a variety of grant instruments.

#### OUTSTANDING INVESTIGATOR AWARD

Dr. DeVita continued by saying that a subcommittee of the President's Cancer Panel, chaired by Dr. Harold Amos, was developing a new instrument--an Outstanding Investigator Award. He explained that this was not a lifetime award but would be designed to provide the investigator with enough time and flexibility to be creative. This award will be made based on the investigator's previous research. After the award is made, the investigator will have four to five years before he must submit a competing renewal application for peer review to determine his productivity and whether to continue funding.

A major problem facing the subcommittee is establishing valid criteria to judge previous research performance. Dr. DeVita discussed the problem of having a single committee review the performance of scientists,

covering a variety of disciplines, and mentioned the option of setting up individual committees for each scientific area of research. He noted, however that this alternative also had potential drawbacks, especially when it came to setting priorities among the different research areas. Dr. DeVita asked for suggestions from the DCT Board that might help solve these evaluation concerns.

### SYNOPSIS OF DISCUSSION

Because a P01 grant has multiple individual investigators, Dr. Efraim Racker asked why each subproject could not count as a separate grant.

Dr. DeVita answered that the NCI was not allowed by the NIH or the Department of Health and Human Services to count subprojects of a P01 grant individually. This would be changing the ground rules of the entire process and in any case would not alter the total number of investigators supported by the NIH. It would just raise the original grant funding target from 5,000 to 6,000, for example.

### III. DCT DIRECTOR'S REPORT - DR. BRUCE A. CHABNER

Dr. Chabner welcomed a new member, Dr. Max Cooper, Professor of Medicine at the University of Alabama, to the Board. He also introduced a guest, Dr. Charles Coltman, who is chairman of the Executive Committee of the Cooperative Group Chairmen.

Dr. Chabner extended the Board's sympathies to the families of two distinguished investigators, Drs. Charles Heidelberger and Sol Spiegelman, who died recently. Dr. Heidelberger was Professor of Biochemistry and

Pathology at the University of Southern California and Director for Basic Research at the Comprehensive Cancer Center. He was a former member of the Board of Scientific Counselors and a leader in cancer therapy research. Dr. Spiegelman was a Professor of Human Genetics and Development at Columbia University College of Physicians and Surgeons and was the Director of the Institute for Cancer Research. He contributed to the development of one of the most important techniques in molecular biology, the hybridization of complementary sequences of DNA and RNA.

Dr. Chabner announced the following changes in the organization of the DCT:

- Dr. Robert Wittes has accepted the position of Associate Director for the Cancer Therapy Evaluation Program.
- Dr. Joost Oppenheim, formerly a Section Chief in the National Institute of Dental Research, will head laboratory efforts in cell-mediated immunoregulation within the Biological Response Modifier Program (BRMP).

Dr. Chabner also announced that the DCT is now recruiting for the position of Associate Director for the Developmental Therapeutics Program. Nominations should be directed to Dr. Chabner or to Dr. Saul Schepartz, who is Chairman of the Search Committee.

#### COMPLIANCE MONITORING OF CLINICAL COOPERATIVE GROUPS

Dr. Chabner stated that the DCT has developed new policies for on-site monitoring of the Clinical Trials Program. Over the past nine months, efforts have been made to verify the accuracy of data collected in clinical trials and to verify that clinical trials conducted by affiliates of the Cooperative Groups conform with Food and Drug Administration (FDA) regulations regarding informed consent, Institutional Review Board

(IRB) approval, recording the use of investigational drugs and reporting of drug side effects.

Dr. Chabner reported that the initial evaluation of satellite investigators has caused some concern about their awareness of the above regulations. (He defined satellite investigators as physicians who are associated with the established cooperative group members, but are not funded members themselves. They do enter patients on group protocols.) Dr. Chabner indicated that he has asked the cooperative group chairmen to help develop uniform guidelines defining satellite membership, and describing how satellite members should participate in clinical trials and what instruction they should receive. He emphasized that satellite investigators using investigational drugs must register with Cooperative Groups and with the FDA and CTEP to receive their FD1573s. In the future, the DCT will include them in the site visit monitoring system on a regular basis.

#### SYNOPSIS OF DISCUSSION

Dr. Philip DiSaia expressed surprise that satellite investigators were deficient in their compliance with regulations. He indicated that at his medical center, affiliated investigators are required to gain permission from the parent institution, and that the parent institution would not activate a clinical trial in a satellite institution unless proper IRB approval is granted. In addition, when a patient is placed on a protocol, the investigator must submit follow-up forms. It was Dr. DiSaia's contention that the parent institution should be responsible for monitoring satellites.

Dr. Chabner replied that although he was unable to discuss the

details of the preliminary findings, significant deficiencies had been identified in some satellites regarding compliance with important elements of the administration of clinical trials. He suggested that the problem arose because many of the affiliate-investigators did not completely understand the relatively complex system of regulations.

Dr. Brigid Leventhal agreed with Dr. DiSaia that monitoring of clinical trials performed by satellite members should be the primary responsibility of the affiliate research institution. If it failed to monitor its satellites, she said, the institution should be judged on that account.

Dr. Chabner agreed with the above comments, but he also stated that monitoring procedures must be in accord with the NCI guidelines and include compliance with FDA regulations. He added that the official relationships between the member and its satellites would be described in the guidelines now being prepared. Dr. Hellman requested that Dr. Chabner present the guidelines to the Board as they are being formulated.

#### GUIDELINES FOR COLLABORATION WITH INDUSTRY

Dr. Chabner discussed the role of the DCT in cooperative research ventures with industry. He stated that the new orphan drug law contains tax advantages for drug companies willing to participate in orphan drug research, including cancer therapy research. He explained that DCT would like to encourage industry participation at all levels in the Drug Development Program and would welcome its help in financing clinical testing through the Cooperative Group Program.

He added that some important aspects of the Government's relationship with industry remain to be resolved. He expressed concern, for

example, about the role that the NCI would play in reviewing protocols, in setting priorities for which drugs were tested, and in regulating clinical trials performed by pharmaceutical firms. Dr. Chabner stated that Dr. Wyngaarden has asked the NIH to develop a policy and guidelines for collaborative research with industry. Dr. Chabner added that he had asked Dr. Schepartz to establish a task force of preclinical and clinical researchers within DCT, Cooperative Group Chairmen and representatives of industry to draft a position statement that the DCT can present to the NCI and the NIH. Dr. Chabner requested that Dr. Hellman nominate a Board representative for this effort.

#### SYNOPSIS OF DISCUSSION

Dr. Gertrude Elion asked whether therapeutic cancer drugs are included under the orphan drug law. Dr. Chabner deferred to Dr. Schepartz who indicated that two specific points were still under discussion: 1) the provisions of the Act and 2) the involvement of industry in drug development and clinical trials, which may result as a consequence of the provisions of the Act.

Dr. Schepartz said that the Orphan Drug Act provided certain incentives for individuals and/or organizations which develop drugs or devices which are effective in the treatment of rare diseases. However, the Act does not define "rare" diseases. An organization (or individual) must apply to the FDA to get a compound designated as an orphan drug before it qualifies for financial benefits. In the absence of an existing patent, the developers of such a compound can obtain an exclusive New Drug Application (NDA) permit for seven years. They can also receive a 50 percent

tax credit on clinical trials they carry out. Dr. Schepartz stated that there was a \$4 million per year grant and contract program to support clinical trial aspects.

Although it is not clear to what extent cancer drug development is covered under the Act, Dr. Schepartz indicated that most scientists would consider specific cancers such as islet cell carcinoma of the pancreas a rare disease, and therefore an effective drug for this disease would qualify as an orphan drug. Dr. Schepartz added that he is one of two NIH representatives on the DHHS Orphan Products Board that will be establishing general guidelines to define "rare" diseases. Dr. Dani Bolognesi asked if biologics were to be included under this act. Dr. Chabner replied that the NIH committee would address this question while reviewing the issues surrounding the relationship of NIH to industry research.

#### CANCER TREATMENT REPORTS

Dr. Chabner described a recent incident related to the publication of an article authored by Dr. Mark Straus in Cancer Treatment Reports (CTR). He indicated that Dr. Straus had submitted a manuscript to CTR describing the results of a chemotherapeutic regimen in patients with advanced prostate cancer. The manuscript was accepted for review by the Editorial Board at a time when there was no formal NIH investigation of Dr. Straus. The manuscript was reviewed and returned to Dr. Straus for revision. During this period, a formal investigation of Dr. Straus was undertaken by the NIH. When the revised manuscript was received, Dr. Straus had been debarred by the NIH, so the CTR Editorial Board decided that verification of the data was necessary before the manuscript could be accepted for publication.

Dr. Straus was asked in October 1981 to have the Dean of his medical school appoint an independent auditor to verify the raw data. After receipt of a letter from a faculty member at his medical school verifying the data, the manuscript was published in CTR in November of 1982.

About three weeks later it was learned that the person who validated the data was not appointed by the Dean and had only reviewed "raw data" on one of 22 patients involved in the study. Dr. Chabner stated that a retraction of editorial endorsement would be published in the January 1983 issue of CTR. He added that in the future, when any suspicion of invalid data in a manuscript existed, a procedure for validating the data would be determined by the Editorial Board and reviewed by the Director, DCT, and by the Executive Committee of the NCI. Only if proper validation was received would the data be considered for publication. Review by the Editorial Board, Dr. Chabner, and the Executive Committee would be required for acceptance.

#### SYNOPSIS OF DISCUSSION

Dr. Paul Calabresi asked if another auditor had subsequently been appointed to validate Dr. Straus' data. Ms. Susan Hubbard indicated that Cancer Treatment Reports would reconsider its position if the raw data were examined and validated by a representative of the New York Medical College. If the actual raw data on all patients included in the article were verified, she indicated that CTR would publish an announcement confirming the validity of the article.

#### NATIONAL DRUG DISCOVERY GROUPS

Dr. Chabner then discussed the current plans for drug discovery groups to develop new anticancer agents under the cooperative agreement

mechanism. This plan was initially proposed by a subcommittee of the Board headed by Dr. Alan Sartorelli, a former Board member. Dr. Chabner indicated that the DCT hoped to fund four groups at a total cost of \$3 million. An initial program announcement attracted about 200 responses. He stated that the DCT will issue a request for application (RFA) in early spring with a goal of awarding the cooperative agreements in March of 1984. He reported that the person to address questions to is Dr. John Venditti in the Development Therapeutics Program (DTP).

#### AIDS

Dr. Chabner reported that the Board had been instrumental in establishing an RFA for research into the cause, treatment and other aspects of Kaposi's sarcoma, a disease associated with acquired immunodeficiency syndrome (AIDS). The RFA was issued about six months ago with a budget of \$1.25 million. Of the 45 responses received, 27 cooperative agreements had been approved. The DCT will bring these applications to the National Cancer Advisory Board for approval to fund those with higher priority scores; some applications had been deferred for site visits.

Dr. Racker asked who had performed the scientific review of these applications. Dr. Chabner answered that a special study section, composed of very distinguished virologists, epidemiologists and cancer treatment specialists, was formed. Dr. Bolognesi then asked about the amount of money that had been obligated for the initial awards. Dr. Chabner replied that the DCT had obligated about \$250,000 of the \$1.25 million. He also stated that if the site visits reveal high quality applications which could bring the total funding requirement above \$1.25 million, additional funds

would be obtained to support awards in this area.

Dr. Chabner stated that a total of 960 cases of AIDS have now been reported in the United States. About 70 percent of these cases were reported in the last year, with an additional 60 cases reported in foreign countries. About 35 percent of these cases also have Kaposi's sarcoma. In addition, a large number of diffuse, large-cell lymphomas have been diagnosed in patients with AIDS, including 10 cases of primary intracerebral lymphomas, a presentation only found in immunosuppressed patients following organ transplants. Dr. Chabner remarked that the New England Journal of Medicine had reported very disturbing alterations in immune function in hemophiliacs, with many having the same inverse ratio of helper to suppressor T-cells in their peripheral blood as observed in AIDS patients. He added that the Center for Disease Control has received an additional appropriation of \$2 million for research in this area.

#### DRUG RESISTANCE

Dr. Chabner then described the activities planned to implement the Board's proposal to support research into the development of models for drug resistance as part of an antitumor screen. He reported that investigators at the University of California have confirmed earlier reports by a Japanese group that resistance in antibiotic-resistant tumor cells can be overcome by pretreatment with verapamil, a calcium channel blocker. He announced that the DCT's Drug Evaluation Branch will hold a symposium on cellular resistance to anti-cancer drugs at the NCI on February 25, 1983.

Dr. Chabner then asked Dr. Robert Shoemaker to describe the arrangements for the conference. Dr. Shoemaker said that registration forms had

been mailed to Board members and interested scientists. Dr. Leventhal suggested inviting Dr. Avner Ramu at Hadassah Hospital in Jerusalem. Dr. Chabner mentioned that he recently visited Dr. Ramu and that Dr. Ramu has had some interesting results with the calcium blocker perhexiline maleate. Dr. Shoemaker indicated that Dr. Ramu had already been invited to the symposium. Dr. John Driscoll reported that Dr. Tsuruo from the Cancer Chemotherapy Center in Japan, who had published the first paper on verapamil, was also a speaker on the agenda.

Dr. Hellman remarked that he received a letter from Dr. James Goldie concerning the problem of screening for drug resistance. He suggested discussing the letter at a Board meeting following the symposium. Dr. Chabner agreed and indicated that the proceedings of the symposium will be published in CTR. He expected to report on the symposium to the Board in June.

#### MEDICAL ONCOLOGY SERVICES

Dr. Chabner reported that the Board has expressed concern that the DCT's two medical oncology branches, one at the Navy Medical Center and the other at the Clinical Center, have overlapping research interests and protocols in Hodgkin's disease, breast cancer, cutaneous T-cell lymphomas and other diseases. He indicated that the DCT is coordinating the research activities of these two branches. Joint staff meetings to discuss clinical protocols, common staging conferences and an exchange of attending physicians were being planned.

Dr. Chabner indicated that he will be an attending physician in the NCI-Navy Medical Oncology Branch in April. He also commented that the Board will make a site visit to the Navy Medical Center in June, with

Dr. Calabresi heading the site visit team.

Dr. DiSaia commented that the site-visit team which had reviewed the Medicine Branch in 1980 had felt that the clinical trials conducted by the Medicine Branch, although very worthwhile, had insufficient patient accrual to constitute proper clinical trials. The team had recommended that the Board consider consolidating the NCI-Navy Medical Branch and the Medicine Branch in order to improve the accrual of patients.

Dr. Chabner indicated that recent cooperation between the two clinical groups had increased the accrual of patients to high priority trials. He also stated that the proposed exchange of senior staff members would enhance the collaborative relationship between the two branches.

When Dr. DiSaia asked why the DCT had not designated one person to be Chief of both branches, Dr. Chabner replied that the two branches are too large for one Chief to administer as that individual would have little time to pursue research interests. In addition, he pointed out that the research activities of the two branches are quite different. The research of the Medical Oncology Branch is focused on molecular biology while the research of the Medicine Branch is focused on drug development and clinical trials.

Dr. Chabner then asked Dr. Samuel Broder to comment further on the issue of combining the operations of the Medicine Branch and the Medical Oncology Branch. Dr. Broder indicated that he would look for advice in this regard from the site visit teams. Upcoming are site visits to the Surgery Branch in April and to the Navy Medical Center/Medical Oncology Branch in June. Dr. Broder also indicated that he was directing many of the strategies to unify the two branches through the Office of the Associate Director.

Dr. Chabner then emphasized that, if the current structure with two medical oncology branches impedes clinical research, the DCT will consolidate the two branches into one. Dr. Hellman added that the Board has only heard from one site visit team, and proper conclusions must await the results of the Navy Medical Center/Medical Oncology Branch site visit. He suggested that the September board meeting might be an opportune time to review the outcome of this visit. Dr. Chabner indicated that at the time of the most recent site visit of the Medicine Branch, the cooperative agreement with the Navy had not been approved. He noted that since the agreement with the Navy was signed in September 1982, cooperation between the two branches has improved. Dr. DiSaia commented that the review of the Medicine Branch was very positive, but the general consensus was that the effectiveness of the two branches could improve by close cooperation in conducting clinical trials.

#### PRIORITIES FOR THE DCT

Dr. Chabner requested questions or comments about the statement of DCT priorities which he made at the last Board meeting and which was distributed by mail to each Board member. The consensus was that the priority of individual items should be discussed as each was considered for implementation.

#### DISTINGUISHED SCIENTIST AWARDS

Dr. Chabner announced that Mr. Paul Davignon, Chief of DCT's Pharmaceutical Resources Branch, had won the Andrew Craigie Award for outstanding accomplishment in advancement of health professional pharmacy

within the Federal Government. In addition, Dr. Robert Gallo of the DCT has received the 1982 Albert and Mary Lasker Award with four other scientists for his discovery of the human T-cell lymphoma/leukemia virus.

#### INTRAMURAL REVIEWS

Dr. Leventhal stated that she was bothered by two statements found in Dr. John Eberhart's report that suggested that the peer review system for intramural projects was different than that for extramural research programs. The implication was that there was less necessity for preplanning and setting of priorities within the Intramural Program. Dr. Chabner answered her concerns by saying that it was the consensus of the NCI scientific directors that all intramural site visits should be rigorous as site visits for extramural ROIs or POIs. He reported that projected plans as well as past performance are reviewed. In fact, the branches are asked to include their plans for the next three years. Dr. Chabner indicated that he does not subscribe to the notion that the intramural review should analyze only past accomplishments.

#### IV. REPORT OF THE SORDS COMMITTEE

Dr. Hellman introduced the attending members of the Surgical Oncology Research Development Subcommittee (SORDS): Dr. DiSaia, Chairman, Drs. E. Carmack Holmes, William Shingleton, William Donegan, Theodore Phillips, Dani Bolognesi, Samuel Wells, John Durant and Ernest deMoss. He stated that the purpose of the committee was to evaluate and stimulate surgical research in oncology. He then asked Dr. DiSaia to present his report.

Dr. DiSaia recalled that the subcommittee was formed at the urging of Dr. Walter Lawrence who recognized the need for the development of surgical oncology research in academic centers because of the significant decline in the number of academically oriented surgical oncologists. He indicated that the most difficult person to recruit for a university cancer program is a surgical oncologist. Dr. DiSaia continued by recalling that several years ago, the DCT had issued a program announcement to encourage surgical research. He pointed out that \$1.2 million were awarded. About one and a half years ago a second announcement for planning grants and research grants (R01s and P01s) was issued. There were 51 responses; seven R01 and one P01 grants were funded. Five P20 exploratory grants were also funded.

Dr. DiSaia then outlined the recommendations of the SORDS that met in October 1982 and on January 26, 1983. The first recommendation was to promote the new Physician Investigator Development Award in the surgical oncology community. Currently, 36 total awards are available per year for medical specialties in short supply. These awards include a salary of \$30,000 a year and \$10,000 in support of research. Physicians who have completed two to eight years of training following the receipt of their medical degree are qualified to apply for these grants. Dr. DiSaia indicated that the Division of Resources, Centers, and Community Activities (DRCCA) will make these awards available to surgical oncology applicants each year. If there are insufficient funds available in DRCCA, DCT will insure sufficient funds to make eight awards if meritorious applications have been received. The announcement for the Physician Investigator Development Awards will appear in the NIH Guide for Grants and Contracts on February 25, 1983.

Dr. DiSaia noted that the second concern of the SORDS was that surgeons often believe that the review of surgically oriented ROIs and POIs is often biased because the study sections teams do not include a sufficient number of surgeons. To correct this situation, last October SORDS asked Dr. Chabner to create a special study section, predominantly of surgeons, to review the ROI and POI applications received in response to the Program Announcement in Surgical Oncology. However, a short time after the SORDS meeting, the NIH dissolved all special study sections. Dr. DiSaia indicated that Dr. Stephen Schiaffino, Deputy Director of the Division of Research Grants (DRG), announced at the SORDS meeting that the Experimental Therapeutics study section would be soon split into a basic research study section and an ad hoc clinical research section. At that meeting, Dr. Schiaffino said that, whenever appropriate, ROIs and POIs dealing with surgical oncology would go to the clinical study section for review. Dr. Schiaffino was interested in receiving names of surgeons who were willing to serve as members of the study section.

Dr. DiSaia stated that the third action taken by the SORD subcommittee was to suggest to Dr. Chabner that surgical oncology be considered an "activity" by the NCI. He reported that Dr. Chabner brought this concept before the Executive Committee of the NCI in December, but action was deferred because only \$3 million of surgical oncology grants could be identified within the DCT. He stated that Dr. Chabner planned to return to the Executive Committee for reconsideration of this proposal this spring.

Dr. DiSaia then addressed a fourth suggestion brought to the SORD subcommittee, the clinical education grant. In recent years, these grants had only provided funds for faculty members involved in curriculum devel-

opment. It was suggested that Dr. Chabner petition the Executive Committee to have these grants include salary stipends for house officers in departments of surgical oncology.

Dr. DiSaia reported that the SORD subcommittee also requested that the DCT consider the possibility of republishing the Program Announcement encouraging surgical oncology grants. He indicated that the SORDS believed that the scope of suggested research stated in the present announcement was too restrictive and recommended that the statement be modified to broaden the announcement beyond research involving a surgical procedure.

Dr. DiSaia also indicated that the SORD subcommittee decided to ask the DCT to reconsider issuing a RFA for P20-like grants. Such grants were awarded to five institutions last year. Dr. Chabner had indicated that Dr. deMoss should obtain feedback from institutions that had received these grants to determine how the money was being utilized to keep young surgeons in an academic environment and to stimulate them to follow a career in surgical oncology. The SORDS members suggested that the DCT bring this proposal for a second RFA for planning grants at its June meeting.

Dr. DiSaia noted the last issue discussed by SORDS was to thank Dr. Hellman for including the SORDS report early on the Board's agenda and to request that this practice continue.

#### SYNOPSIS OF DISCUSSION

To emphasize the importance of surgical oncology, Dr. Holmes commented that a recent retrospective study conducted by one of the Cooperative Groups found that the effect of adjuvant therapy was totally obscured

by the inadequate quality of the surgery performed. He emphasized that this illustrated the need to have quality surgery for successful clinical trials with solid tumors.

Dr. Shingleton agreed with the report that Dr. DiSaia presented. He felt the perception that the surgeon was not a fully participating member of the multidisciplinary research team was correct. He agreed that any and all mechanisms described by Dr. DiSaia would be helpful to the development of surgical oncology research. Dr. Durant indicated that he agreed with every point made and stressed that the Board should make a long-term commitment to solve the problems discussed. Dr. Carol Portlock and Dr. Racker then asked for a definition of a surgical oncologist. Dr. Hellman replied that he favored a broad definition that included scientists ranging in expertise from a gynecologist to a biochemist in a Department of Surgery.

Dr. Hellman asked Dr. DiSaia if there was some affirmative action planned to assure that at least eight Physician Investigator Development Awards went to acceptable candidates. Dr. Chabner assured him that eight out of a pool of 36 awards were expected. Dr. Wells asked if the level of funding was fixed for these awards and if the eligibility requirements of training beyond the medical degree could be stretched to nine years. Dr. Chabner replied that there is no flexibility in terms of salary, which is \$30,000 for three years, but not everyone will get the full \$10,000 for research support unless they apply for it. He indicated that if the residency was unduly long, the guidelines were sufficiently flexible to stretch the eligibility requirement to the ninth year. Dr. Shingleton asked if the DRCCA and the DCT plan to continue the Physician Investigator

Development Awards over a period of years and, if so, at what level of funding. Dr. Chabner replied that while the awards were subject to the same budget constraints as everything else, plans were to maintain the proposed level of funding.

Dr. Hellman then requested Dr. Chabner to expand on what was meant by adequate surgical representation on the newly proposed clinical study section. He also asked if all surgical oncology grants would go there. Dr. Chabner replied that the Experimental Therapeutics Study Section, which reviews a major portion of preclinical and clinical grant applications directed at cancer treatment, is being divided into two subgroups. Clinical applications will be directed to the clinically-oriented study section. Dr. DiSaia added that the members of the Board should send him any recommendations for surgeons to serve on this new group.

Dr. Hellman asked for a definition of program "activity." Dr. Chabner explained that grants in the NCI are under the supervision of program directors. These directors are responsible for overseeing the review process. They act as advocates for grants in a given area of research or "activity." Hence, by establishing surgical oncology as an activity, it will have a director who can identify any grant that deserves consideration as a funding exception. Dr. DiSaia thereupon moved that the Board endorse the concept of defining surgical oncology as a program activity and suggested that Dr. Chabner ask the Executive Committee to reconsider this proposal as endorsed by the Board. The motion was seconded by Dr. Horwitz and approved unanimously.

Dr. Chabner indicated that Dr. DeVita was willing to consider surgical oncology curriculum development as a target area for DRCCA clinical

education grants. Dr. DiSaia then moved that Dr. Chabner bring this matter to the attention of the Executive Committee. The motion was seconded by Dr. Horwitz and approved. Dr. Calabresi moved and Dr. Wells seconded that at least eight Physician Investigator Development Awards be made available per year. This motion was also approved.

Dr. Hellman then opened a discussion on republishing the current ongoing surgical oncology program announcement with modifications in the statement about surgical research. He noted that program announcements do not have budgetary set asides and that applicants compete in the grant pool. The discussion then turned to the issuance of a second RFA for surgical oncology planning grants. Dr. DiSaia pointed out that the SORDS members thought that the last RFA which funded five planning grants was too small and suggested a larger set-aside. He reported that Dr. Chabner had informed the SORDS that it would not be possible to issue a new RFA until the June Board meeting when the Board could be presented an RFA proposal for concept approval. Dr. Chabner emphasized that the payline had been stretched down to a priority score of 204 to cover the \$0.5 million. He noted that this was 19 points below the payline for the institute. Dr. Chabner recommended that the Board review the expenditures that had been made in the five planning grants that had been funded.

Dr. DiSaia commented that he had received a letter from Dr. John Durant suggesting that the ad hoc study section set up to score these surgical oncology planning grants had criticized the grant applications for not having research elements, although these planning grants were not supposed to contain research elements. Dr. DiSaia felt that the relatively poor priority score assigned to these grants was due to this confusion.

Dr. Chabner emphasized the need to have a well written RFA to avoid such confusion. Dr. Hellman indicated that the DCT program staff should work with the SORDS to prepare an RFA to be presented to the Board in June.

Dr. DiSaia thanked Dr. Chabner and his staff for their efforts to develop new fund instruments to promote the development of surgical oncology research.

#### APPROVAL OF MINUTES

Realizing that the minutes from the previous Board meeting had not been approved, Dr. Hellman asked for approval of the minutes of the October meeting. The motion was approved unanimously.

#### DCT DIRECTOR'S REPORT (Continued) - DR. BRUCE A. CHABNER

##### NCI AND DCT BUDGET

Dr. Chabner presented the Board with an update of the Division's budget and indicated that no major budget decisions were necessary at this meeting.

Dr. Chabner reported that Congress had passed a continuing resolution for \$983 million for the NCI, a \$28 million increase over the \$955 million allocated in the President's FY 1983 Budget and a \$40 million increase over the 1982 level of funding. However, he reported learning at a recent NCI Director's retreat that less than \$6 million of the apparent \$40 million increase remained for distribution to the Divisions after the NCI reached its target for research grants, restored indirect costs and met obligations in Cancer Control. He referred members to Dr. DeVita's earlier discussion pertaining to how the additional monies were being allocated.

Dr. Chabner indicated that the DCT budget he presented to the Board of Scientific Counselors in October 1982 was \$282 million and that it was revised as of January 1 to \$275 million.

Dr. Chabner then reviewed recent trends in the NCI and the DCT budgets. Since 1979, the NCI research projects pool has increased faster than the other budget items, increasing 30 percent over the four years. The NCI budget for contracts during that time has decreased from \$200 million to \$130 million. The Intramural Program budget has increased slowly, from about \$100 million to \$130 million.

Dr. Chabner reported that the DCT budget has increased 13 percent since 1979, from \$244 million to \$275 million. The 1983 estimate of \$275 million represents a \$6 million net increase over the 1982 budget. Of the total DCT budget, \$132 million have been allotted for grants administered by the DCT. The original estimate for all DCT grants in FY 1983 was 135.6 million, but the current estimate was \$132 million, a 35 percent increase from the 1979 figure of \$98 million for this mechanism. He also stated that the current estimate for the total number of grantees funded was 756 compared to 755 for last year; the final number will probably be higher because of the increased money in the grants pool.

Dr. Chabner noted that the DCT's P01 grants have levelled off since 1981, and the current funding was estimated at about \$58 million. He also stated, however, that P01 funding estimates have fluctuated considerably, since the funding of one large P01 grant can change the budget required to cover grants by \$1 million to \$1.5 million. Dr. Chabner expected that the P01 pool may top the current estimate of \$58 million and eventually reach the low to mid-sixties.

Dr. Chabner informed the Board that the overall funding of R01 grants by the DCT was now estimated to reach 29 percent as compared to last year's level of 31 percent funding. With some additional funds expected, he predicted the percentage will be somewhere between the two. He added that the NCAB is faced with the decision of changing the payline or increasing the percentage of funding for each grant.

In reference to the apparent compression of priority scores in recent years, Dr. Chabner stated that he and the program staff had discussed whether the system of reviewing and funding grant proposals needed to be changed. It was decided that the system did not need to be changed but that program staff must follow both the average priority score and the percentage of grants recommended for payment by each study section. Dr. Chabner noted that with the current level of compression, it is estimated that for each point the payline is changed, \$3 million of R01 grants are affected. (In the past, one percentage point would affect only about \$1 million of funding.)

Dr. Chabner reported that contract funding within the DCT has decreased more than 30 percent since 1979. The 1983 figure is \$57 million compared to \$78 million four years ago. He said part of this decrease (\$5.5 million) is due to the transfer of intramural components of the Frederick budget to the in-house line, but most is due to a real decrease in contracts. Dr. Chabner pointed out that the Drug Development Contract Program has been reduced by about 25 percent since 1978 and is now at \$33.9 million. He stressed that if further cuts were were made, they would hamper DTP's research efforts in drug acquisition, screening, formulation and toxicology. He added that funding for the Clinical Trials Pro-

gram and for contracts in support of the Intramural Program has decreased by \$3.1 million and \$1.6 million, respectively.

Dr. Chabner stated that cooperative agreements have increased about 33 percent from 1979 to the present. He also stated that some of this increase was due to a shift in mechanism and cited for example the fact that about \$5 million in clinical trials contracts had been converted to cooperative agreements. Dr. Chabner also noted in regard to the cooperative agreements that the \$200,000 earmarked for Kaposi's sarcoma would be funded from the Institute rather than the Division's budget.

Dr. Chabner reported that intramural research funding has increased 20 percent since 1979. He stated, however, that funds for 1983 were less than those budgeted for 1982; if one takes into account the \$3.3 million that was transferred from this category, the 1983 intramural budget actually decreased by \$1.3 million.

Dr. Chabner then referred to the breakdown of the DCT funding into grant activity areas and noted several changes. He reported that the October estimate for the Biochemistry and Pharmacology Program of \$32.3 million was reduced in January to \$31 million. He indicated there was a good possibility that at least one major P01 grant would be approved and that may bring the funding above the October 1982 estimate. He noted that the January estimate for the Clinical Oncology Program was also less than the October estimate but that there was a \$2 million P01 pending that could raise this item considerably. Dr. Chabner noted that a \$1.6 million increase in funding for Diagnostic Imaging activities was due to the transfer of \$4.4 million in grants from the National Institute of General Sciences (NIGMS).

Dr. Chabner concluded his presentation by noting that there were currently, on board or projected to be on board by the end of FY 1983, 430 people employed by the Intramural Program. There are also 200 people involved in the management of Extramural Program, bringing the total for the Division to 640. He then requested questions and comments on the budget.

#### SYNOPSIS OF DISCUSSION

Dr. DiSaia asked if the DCT had an additional \$2 million that would be distributed to ongoing grantees. Dr. Chabner indicated that there was an additional \$750,000, rather than \$2 million, and that that had been budgeted for the clinical trials monitoring program.

There were no other comments or questions about the budget, and the group adjourned for lunch.

#### V. OBSERVATIONAL STUDIES AND RANDOMIZED TRIALS

Dr. Hellman opened the afternoon session by clarifying the schedule of future meeting dates and asked Dr. Chabner to introduce the discussion on the comparative validity of randomized prospective clinical trials versus observational studies in evaluating the efficacy of cancer treatments.

Dr. Chabner stated that the interest in looking at alternatives to randomized prospective clinical trials arose out of Dr. Alvan Feinstein's recent presentation at NIH on case control methods. Dr. Chabner stated that the attractiveness of observational studies lies in the possibility of conserving resources by reducing sample size and in addressing DCT's concerns about some of the ethical questions that had been raised in the use of prospectively randomized trials. Dr. Chabner pointed out that

there is an ongoing debate in the oncology community about the ethical issues surrounding randomized assignment to a treatment when a strong suspicion exists that an alternative therapy is more effective.

Dr. Chabner also stated that he thought it would be useful for the Board to hear various viewpoints regarding the value of observational studies vis-a-vis randomized trials so that the Board could advise him about strategies for future clinical trials supported by the clinical trial network of the Division.

Dr. Chabner asked Dr. Richard Simon to chair the discussion and proceeded to introduce Dr. Feinstein.

#### OBSERVATIONAL METHODS - DR. ALVAN FEINSTEIN

Dr. Feinstein opened his presentation by saying he would discuss observational studies rather than the more specific case control model. He explained that he still considered the randomized trial method the definitive standard for evaluation of cause-effect issues. With that caveat, he said he would try to clarify circumstances influencing the choice of study methods and, when randomized clinical trials were not possible, to discover how best to approximate the rigor of this method using observational studies.

Dr. Feinstein began by discussing circumstances in which randomized trials are difficult, if not impossible, to apply. The first situation he cited was that in which therapy is unstable and in which new therapeutic approaches that appear to be more effective become available before the completion of an ongoing clinical trial. He gave an example from coronary heart disease treatment studies in which some tunnel implants were abandoned for bypass grafts, and some of these in turn were abandoned for the

percutaneous angioplasty. He noted that in such changing and unstable situations randomized trials applied to the first treatment are compromised by the second and sometimes third treatment instituted.

Dr. Feinstein then stated that a second difficult situation is one in which multiple therapeutic agents are available and the investigator must decide which of the many agents to put into clinical trial. A third situation involves studying the long-term adverse effects of new treatments. To use randomized techniques, a very large sample of patients (often difficult to obtain) is required for the follow-up necessary to observe the long-term adverse effects.

Dr. Feinstein noted that the next difficult situation in which to use randomized trials is the evaluation of new diagnostic techniques. First, changes in technology occur so rapidly that new agents are discovered before the results of previous agents are discerned. Second, because diagnostic agents provide information to make other decisions besides diagnosis, the trials are extremely difficult to design and conduct.

Dr. Feinstein noted also that prophylactic studies do not lend themselves well to randomized trials. He stated that this was because they involve a heterogeneous population, are costly and cumbersome in terms of logistics and require a long period of follow-up and a large sample to detect a small change in the incidence of a disease.

Finally, Dr. Feinstein stated that ethical considerations make it difficult to use randomized trials for the evaluation of suspected noxious agents, even with informed consent.

Dr. Feinstein then turned to a discussion of the purpose of, and

misconceptions about, randomization. One misconception he noted was that randomization is a crucial element of science. A second is that it is required for tests of statistical significance. A third misconception he noted is that randomization is a prerequisite for high quality data.

Dr. Feinstein challenged each of these misconceptions and explained that the main scientific role of randomization, in contrast to its mathematical roles, is to remove personal bias in the selection or the assignment of the variables under comparison.

Dr. Feinstein then discussed some of the clinical phenomena which influence susceptibility bias and outlined several ways of dealing with such bias. Among clinical phenomena influencing bias are the severity of symptoms, the severity of co-morbid associated diseases, the duration of illness and the rate of progression of the disease. He noted that clinicians may consider all of these attributes when deciding whether to assign patients to one therapy or not to assign them at all.

Dr. Feinstein indicated there were also unique situations when therapies produce disparate results in different clinical subgroups. He said that if the clinical distinctions of these subgroups are not identified, the results may be difficult to apply to future patients, and wrong conclusions may be drawn regarding the efficacy of treatment, particularly if synergistic but opposing effects in different subgroups exist.

Dr. Feinstein stated that for these reasons it is important, even in randomized trials, to identify the prognostic categories before therapy. To make randomized groups more precise, prognostic groups should be created using multivariate analyses, and then stratified analyses should be performed by comparing the results of treatment within similar subgroups.

Dr. Feinstein proceeded to point out that susceptibility bias can be removed in this same way even if randomization is not employed in experimental design. He stated that if all the variables that affect therapeutic judgment and prognosis are accounted for, the clinician can determine the impact of any variables that are suspected as important. The need is to identify and include known, but unused variables, such as disease severity and co-morbidity, in statistical analyses. A need also exists to improve biostatistical methods for analyzing multiple variables and to develop improved clinimetric methods that give indices analogous to the APGAR score [used for rating the general well-being of the newborn] or the TNM staging [of carcinoma].

Dr. Feinstein further stated that, even if patients are organized into prognostic groups, randomized and nonrandomized comparisons may still contain bias. For example, differences may exist in the compliance with which the drugs are taken, in the skill of surgeons, or in the use of additional or supportive therapy. The latter is a particularly important hazard when concurrent historical controls are used, since historical controls represent a much earlier treatment that may not have been accompanied by the same ancillary supportive services.

Dr. Feinstein stated that another type of bias that may affect randomized or nonrandomized comparisons is bias in detecting outcome events. This kind of bias is caused by differences in the surveillance of patients, such as the ordering of tests or interpretation of results. This is presumably reduced or eliminated by double-blind procedures. However, he noted that these procedures are not always possible.

Dr. Feinstein indicated that two approaches exist in the design

and analysis of randomized trials, the "fastidious" and the "pragmatic." For example, the fastidious investigator would count all patients receiving a certain agent as part of the treatment group, even if they did not take the agent, took it irregularly, or received other treatments as a substitute. The pragmatic approach, on the other hand, allows the experimenter to ask questions that take into account the complexity of clinical practice in an attempt to analyze distinctions in the proficiency of therapy and detection of outcomes. He noted that both of the approaches are legitimate and can be justified but that they are decidedly different. Studies that are designed and analyzed with one approach may provoke conflict when evaluated by researchers who adhere to the other approach.

In conclusion, Dr. Feinstein outlined ways of improving scientific rigor when using non-randomized design. He suggested that non-randomized comparisons could be improved first by choosing an appropriate zero-time in each patient's clinical course, and second by classifying the patient's zero-state condition according to only those data that are available at zero-time. Third, only those patients who fulfill the eligibility criteria for a randomized trial should be compared. Finally, comparisons should be performed using improved classification and measurement of variables to assess prognosis and proficiency of treatment and to detect outcomes. There is a need to improve the clinimetric measurement scales for clinical observations and to develop criteria for the use of the scales so as to allow data to be reproduced.

#### SYNOPSIS OF DISCUSSION

Dr. Leventhal asked what comparisons would be made after the measure-

ments were completed. Dr. Feinstein replied that the physician would still compare treatment A versus treatment B but would subdivide and classify patients into groups to insure that the proficiency of therapy and the detection of outcome events were unbiased.

Dr. Hellman inquired about the use of retrospective versus prospective data and the use of patients from the same institutions versus other institutions. To avoid ambiguity, Dr. Feinstein defined prospective studies as forward directed, or longitudinal cohort studies, and retrospective as case control studies in which the investigator started at the end and worked backwards. He indicated that case control studies were not used for studying new kinds of treatment, because individuals exposed to the treatment under study were usually not available. He pointed out that the case control method was often useful to reduce sample size. Dr. Feinstein believed that in cancer studies case control studies may be unnecessary because of the high death rates within a relatively short period of observation. Observational cohort studies could be used instead. Dr. Feinstein then explained that similar patients at different institutions could be pooled if the similarities and distinctions ordinarily masked by institutional differences were reduced by better clinimetric classification and measurement procedures.

Dr. Hellman asked what mechanism could be used for comparing groups when there were so many variables for which to account and control. Dr. Feinstein replied that comparison groups first have to be formed using score similarities on specific variables or by data clustering. For example, starting with the TNM cancer staging, which is an example of clustering, clinical variables can be added using discrete data that may

have been compressed in the development of the three TNM stages. This will form a more homogeneous prognostic stratification.

Dr. Portlock asked about the proper use of historical controls. Dr. Feinstein replied that he did not object to using historical controls if distinctions in prognostic susceptibility and measures of proficiency of treatment were identifiable. Dr. Feinstein stated that otherwise he preferred concurrent controls.

#### RANDOMIZED CLINICAL TRIALS - DR. CHARLES MOERTEL

Dr. Moertel began his presentation with a caution about retrospective observational studies. He stressed that it was difficult to select patients with truly identical zero points in these studies. For an example, he described a study published in Cancer which attempted to prove that a moderately high dose of radiation was effective treatment for locally unresectable carcinoma of the pancreas. The author compared an experimental group of patients having localized disease with a historical control group made up of patients half of whom had widespread distant metastases and the rest in poor general condition. Dr. Moertel indicated that this was an improper comparison because the control group could not tolerate two-and-a-half months of radiation given to the experimental group. Therefore, the zero points were entirely different for the two populations. Dr. Moertel then proceeded to review examples of reported cancer studies which he believed were inappropriate use of the historical case control method.

Dr. Moertel stated, however, that a poorly conducted randomized trial could be far more damaging than a historical control trial. He indicated

that multiple-institution trials had provided examples of this. In one study, 75 percent of the good performance status patients were entered by one of the six participating institutions. Five of the six positive responses in previously treated advanced gastric cancer patients were obtained by only one institution. The results obtained by the other five institutions were entirely negative. In a similar study, testing a combination of 5-FU and methyl CCNU, about 15 to 30 percent of the patients randomized were lost due to quality control problems and incomplete surgical removal of the cancer. He described other examples of poorly conducted randomized clinical trials.

Dr. Moertel indicated that quality control problems which include poor quality patient entries and research performance were not unique. He indicated that major quality problems were often as high as 30 percent and minor problems in protocol compliance ran as high as 60 to 90 percent in a group of recently completed GI cancer studies in major cooperative groups. He concluded that the frequency of problems in quality of cancer clinical trials makes the results of many extensive and time consuming trials highly questionable. Dr. Moertel stated, however, that considering the number of variables in human cancer trials and the innumerable sources of hidden bias, it is important to continue advocating high quality concurrently randomized trials in preference to other methods.

#### SYNOPSIS OF DISCUSSION

Dr. Feinstein commented that the issues Dr. Moertel raised about the quality of randomized trials were often clinimetric issues. He agreed that better clinimetric approaches for analyzing data are required to

deal with problems in quality control. He mentioned that another difficulty with contemporary clinimetric approaches is that they do not deal with the quality of life. In some studies, an interested person can only find out whether patients are alive or dead. Issues in the relief of symptoms and the quality of life are totally overlooked because such data are considered "soft." He emphasized that in future studies it is crucial to pay more clinimetric attention to what is happening to the patients as well as to the cancers.

#### CLINICAL TRIAL MODELING - DR. EMIL J. FREIREICH

Dr. Freireich prefaced his talk by stating that funding for investigating the methods of clinical trials has been neglected. He indicated that very little progress has been made in clinical trials methodology since he performed a study of adjuvant chemotherapy involving children with acute leukemia over 20 years ago. An important objective of an innovative clinical trial is not just to determine whether treatment A is better than treatment B but how good is A and how good is B.

Dr. Freireich then began his formal presentation by noting that in studies of acute leukemia there was a qualitatively different outcome for patients who achieved one complete remission and those who did not. Patients who failed to achieve complete remission had a survival experience which was indistinguishable from all the historical data.

Dr. Freireich indicated that his research since 1973 clearly showed that an acute leukemia patient's response to chemotherapy was predictable. He noted that his clinic has developed a logistic regression model for predicting a patient's response to conventional four-drug combination chemo-

therapy. He stated that data from 325 patients were used to derive the model. When a leukemia patient was admitted, six quantitative variables were read across a nomogram and an exact prediction of the probability of response was obtained. Furthermore, when the model was tested on each patient from the original data base prior to receiving treatment, the predicted responses correlated very well with the observed outcome.

Dr. Freireich then explained the strategy his clinic uses in applying the model to the testing of new treatments. Experimental treatments were used in patients who have a low probability of response to conventional treatment. His studies showed that for conventional treatments the O/E ratio (proportion of observed to expected) was typically 1.0, confirming the modeling procedure. The investigational treatment demonstrated an O/E ratio of 1.35, which means that a third more of the patients achieved a complete remission than expected, a statistically significant result and suggested that the treatment was a candidate for front-line treatment. Dr. Freireich cautioned that this result was not an estimate of how much better the treatment was, because data were not yet available on the quality and length of survival.

Dr. Freireich emphasized that continued chemotherapy was indicated in leukemia because in the absence of treatment, relapses occurred in a large majority of patients.

Dr. Freireich then discussed typical periods of remission and probability of relapse. In one group of 207 patients the median duration of remission was approximately 12 to 14 months. He indicated that his research group has formulated a model for predicting the probability of relapse in those patients on maintenance therapy. Two important factors

surfaced during the development of the model. One was that all the variables used to predict the quality of survival were different from those which predict the probability of response to initial treatment. It also became apparent that it was important to continue to collect additional data on the patients while they were in remission. He indicated that variables which were not statistically significant for one year disease-free survival or one year remission were very powerful for predicting long-term survivorship.

Dr. Freireich announced that his group has recently developed, but not yet published, a specific model for predicting recurrence within the first year. The object of this exercise was to identify the patients who were at greater risk of relapse and to introduce an innovative treatment at that point.

Dr. Freireich then showed the preliminary results of applying the one-year model to therapy by bone marrow transplantation and to AMSA-OAP and to conventional treatment. Patients who had poor prognosis for remaining in remission for one year received bone marrow transplants. Patients who were favorable for remission induction, but likely to relapse, received AMSA-OAP treatment. Patients who were favorable for both remission induction and for remaining in remission received conventional treatment. Dr. Freireich indicated that the O/E for patients receiving conventional treatment was 0.96, as predicted. Interestingly, the patients who were favorable for induction but likely to relapse had a O/E ratio of 1.6 after treatment with AMSA-OAP. He suggested that the sequence of AD-OAP induction followed by AMSA-OAP maintenance was promising and merits confirmation. Patients who had poor prognosis for induction, went into

remission and were maintained on AMSA-OAP had an O/E ratio of 1.0. Data on the bone marrow transplants suggested its superiority as a treatment method but Dr. Freireich warned that results of the bone marrow transplants were preliminary and to a certain degree limited in that only eight patients had been treated. He stated that, if the known elements of bias were taken into consideration, transplantation appears as effective as chemotherapy. Dr. Freireich stated that he was still systematically studying this proposition.

Dr. Freireich summarized that these models were effective tools in selecting candidates for front line treatment and for developing salvage strategies for detecting new treatments. As more prognostic variables are identified, the models become more specific. For example, the variables which were used in a model that predicted for AMSA response were not useful in predicting response to conventional treatment.

Dr. Freireich then stated that the clinical trial methodology is, in his opinion, the most important area for DCT to fund. To make his point, Dr. Freireich stated that in every scientific discipline, the studies that are highly cited are the methodology papers since they are crucial in generating new knowledge. He noted that one variable in clinical trials that is difficult to quantitate and evaluate is the quality of the physician.

In conclusion, he stressed that the practitioner must remember that in clinical trials it is important to determine not only which treatments are effective, but also what type of patients are likely to benefit from conventional treatment and which ones should be subjected to innovative methods from the start.

## SYNOPSIS OF DISCUSSION

Dr. DiSaia asked if Dr. Freireich would relate his experience with historically controlled comparisons and prospective randomized trials. Dr. Freireich replied that it was easy to find weaknesses in clinical trials. The important question was whether the trial was done professionally and whether the outcome influences future work. He emphasized that the basis of science was not the quality of the procedure used, but verification, and the continued verification of data is essential. He stated that the problems with randomized trials were as serious as the problems with historical control trials. He felt that historical control trials have in the past, and will in the future, significantly influence the choice of treatment.

## CLINICAL TRIAL BIOMETRICS - DR. RICHARD SIMON

Instead of his written presentation, Dr. Simon addressed more specifically the issues surrounding the research methods presented by the previous speakers.

Dr. Simon agreed with Dr. Freirich's assertion that clinical trial methodology ought to receive more funding. He stated that studying prognostic factors and doing innovative experiments are not in conflict with randomized clinical trial methodology. The reason for randomization is to control the potential bias caused by factors that are not well understood. Dr. Simon indicated that a critical question is: "To what extent does the researcher understand the prognostic factors in a specific kind of cancer?" If prognostic factors were well understood, the sample size of randomized clinical trials could be decreased drastically. Dr. Simon

explained that the reason clinical trials are so large is that the known prognostic factors do not explain most of the variability in the outcome of the study.

To illustrate his point, Dr. Simon used the results of a coronary drug project. In a double blind national study, patients who took their placebo less than 80 percent of the time had a five-year mortality rate of 28 percent; those who took it more than 80 percent of the time had a mortality rate of only 15 percent. The investigators included about 45 baseline prognostic factors in a multivariate regression analysis in order to explain this difference. No matter how hard the investigators tried, they could not get a significant p value. Dr. Simon suggested that some explanatory variables were apparently not accounted for. Dr. Simon noted that randomization is not the solution for all of the problems associated with clinical trials; it cannot determine which treatment is best for whom, and it cannot prevent the loss of some patients to human error. However, Dr. Simon was not convinced that observational studies provide a good alternative to clinical studies.

#### SYNOPSIS OF DISCUSSION

Dr. Feinstein commented that prognostic studies are weak when they continue to use the same set of unsatisfactory variables. The number of variables and the sophistication of the mathematical analysis are no substitute for recognizing and including the pivotally important prognostic variables. To illustrate this he expanded his previous example of the placebo phenomenon by stating that it is now generally accepted that various aspects of people's psyche determine how well they are going to

live and how well they comply with various drug regimens. He emphasized that the problem with many clinical trials often is that many clinical distinctions and decisions were systematically omitted from the list of prognostic variables.

Dr. Portlock asked Dr. Feinstein if his data set was more valid than Dr. Freireich's data set. Dr. Feinstein replied that if an investigator showed major prognostic distinctions within any morphological group, then they were more precise. For example, if a clinician treating breast cancer paid attention to a woman's story of how long she has had the lump, he could distinguish between groups of patients with slow growing cancers and other groups with rapidly growing cancers and use these distinctions in his research. Dr. Freireich remarked that it was very important that all the objective data obtained from the patients were reported so that the kinds of comparisons that follow were not applied to entirely different patients (e.g., Morton's series to Moertel's series, etc.). Dr. Feinstein emphasized that the quality of reporting the identified prognostic information in scientific publications was very important.

Dr. Portlock suggested that a good clinical trial was often traceable to the initial acquisition of the patients for the trial, making certain that the patients had good performance status and a good initial evaluation. Dr. Leventhal commented that a problem existed in the standardization of eligibility criteria for accepting patients in clinical trials. She added that another area of deficiency was diagnostic methodology.

Dr. Chabner emphasized that it was a mistake to discard the idea of the observational trials and that Dr. Freireich's work was a reasonable

approach, and a viable alternative to the randomized trial. He suggested that scientists performing site visits ought to pay close attention to the percentages of ineligible patients and percentages of patients receiving the therapy prescribed by protocol. Dr. Chabner also commented that there was not much discussion about the possibility of using the alternative of observational trials with carefully matched historical controls in some of the trials the DCT was supporting.

Dr. Phillips commented that Dr. Moertel made an error by lumping patients who dropped out because they died or refused further therapy with ineligible patients but agreed with the general consensus that randomization was not an alternative to collecting detailed data. Dr. Feinstein echoed the sentiments of previous speakers by suggesting that some of the problems seen in the quality of clinical trials were the result of investigators becoming complacent. Dr. Freireich stated that randomization did not necessarily eliminate physician bias, institutional bias, and other unknown variables introduced in large cooperative studies. He also stressed that randomization was conceptually introduced to assure comparability between two different groups of individuals. In response to an earlier question by Dr. Hellman as to whether it was prudent to support the large-scale randomized clinical trials with the present financial restrictions, Dr. Phillips said that in his view, the DCT should focus its attention on innovation and only use the expensive randomized trial for very limited kinds of studies.

Dr. Chabner concluded the discussion by stating that with the Board's advice, DCT will explore how we can incorporate the observational type of trial with historical controls and utilize it to a greater extent in the

clinical trials network. Dr. Hellman agreed that this was just the beginning of discussions on this topic.

VI. CONCEPT REVIEW - DR. BRUCE A. CHABNER

Dr. Chabner began the discussion by stating that the purpose of the concept review was to assess whether the general scope of a project was appropriate, whether funds were sufficient to support it, whether the suggested time interval was appropriate and whether the objectives had scientific merit.

Technical Support for Slide Preparation for the Testicular Intergroup Study: Proposed new resource contract with a first year award of \$12,000; period of two years. Dr. Daniel Hoth explained that the purpose of this interagency agreement was to supply the services of a technician to perform slide block preparations of pathologic materials received from participating clinical centers. This was part of an Intergroup Stage I and II Testicular Cancer Protocol. The technician was supervised by Dr. Mostofi, an expert pathologist who was contributing his services without charge to this project.

Dr. Calabresi moved for approval and the motion was seconded. The Board voted for approval.

Feasibility Study for the Acquisition, Quality Assurance, and Distribution of Biological Response Modifiers: Proposed new resource contract; period of one year; award ceiling of \$200,000. Dr. Robert Oldham indicated that the original plan to establish an acquisition/distribution system for biologic response modifiers (BRMs) was presented to the Board at the June 1982 meeting. At that time, the Board felt that the proposed project

was too large and lacking in specific details. The Board requested that the Biological Response Modifiers Program (BRMP) staff provide more detailed information before completing the concept review. On August 31, 1982, the BRMP sponsored a retreat consisting of BRMP staff, extramural scientists from academia and industry and Decision Network Committee members to discuss the BRM acquisition/distribution program. The recommendation of the retreat participants was to award a survey contract to clarify several questions. Areas requiring clarification were: the number of requests anticipated for BRMs, the most effective management for BRM distribution, mechanism of cost reimbursement to pay for BRMs, quality assurance, cooperation of pharmaceutical firms and other suppliers, confidentiality, best method of storing and distributing BRMs, and the cost of such a system.

In response to these recommendations, Dr. Oldham asked the Board for approval of a one-year contract with a ceiling cost estimated at \$200,000 to answer the questions on scope, size, and type of acquisition and distribution system that might be most useful to the research community.

Dr. Marks asked whether the purpose of the contract was to determine what BRMs now exist that meet certain criteria of quality, efficacy and toxicity. Dr. Oldham replied that the purpose of the survey contract was to discover what BRMs were available, and whether universities or pharmaceutical companies were interested in sharing these agents and under what conditions. When Dr. Marks suggested that a request letter may accomplish this at lower cost, Dr. Oldham replied that the members of the retreat felt that a questionnaire could not provide the extensive information required to answer the complex issues involved. One issue that

could present problems was the confidentiality requirements of the pharmaceutical industry.

Dr. Racker asked how many BRMs were potentially available.

Dr. Oldham replied that there were thousands of BRMs, and as an example, he indicated that every monoclonal antibody was a potential therapeutic agent.

Dr. Paul Calabresi asked for more specific information on how the money would be allocated. Dr. Oldham explained the money would support two doctoral level individuals, appropriate support staff and travel funds for visits to companies and institutions. Dr. Calabresi then asked if the forthcoming answers were expected to maintain their relevance for a long period of time. Dr. Oldham indicated that there were considerable changes expected in this area. However, the RFP will require the contractors to provide not only current information but a projection over the next 5 to 10 years. They would also evaluate whether the initial program cost estimates of \$1 to \$2 million were defensible.

Dr. Bolognesi commented that the purpose of the investment, as he understood it, was not to try to identify which biologicals were now available but was to provide a mechanism for acquiring and distributing BRMs as they became available. Dr. Cooper indicated that he felt that the project had great potential and it was a reasonable investment.

Dr. Horwitz asked what types of BRMs were currently on hand and if they were distributed to other scientists. Dr. Oldham replied that the BRMP has only a few on hand, because no system was in place to acquire, store, evaluate or distribute them. The only biologicals that are available currently are those made by the intramural program and the collabo-

rative fermentation plant. A few BRMs like Interferon have been purchased specifically for clinical trials.

Dr. Goodman indicated that he thought an acquisition/distribution system was a reasonable concept with the potential of growing as large as the Drug Development Program. Dr. Elion cautioned that it was important to select experienced scientists to function as DCT's liaisons with universities and pharmaceutical companies. She interjected that qualified scientists may not want to undertake the task for a single year. Dr. Marks stated a lack of confidence that \$200,000 was enough to implement such a sophisticated and large project if, in fact, the concept was to develop some knowledge of the universe of BRMs. Dr. Hellman replied that it was not intended to be an in-depth study of the agents; rather it was a feasibility exercise to develop a mechanism to handle a large number of different kinds of BRMs. Dr. Oldham explained that the purpose of the contract was to survey various institutions and companies to determine how many BRMs they were willing to share through a government sponsored system. After the availability requirements were gathered from all sources, the contractor would be expected to assemble the data in a way that the NCI could develop a functional system for implementing this working concept.

Dr. Calabresi asked if Dr. Chabner viewed this project as a feasibility study. Dr. Chabner replied that it was not a feasibility study. It was an information gathering activity to identify sources and availability of BRMs and to determine whether there was a demand for them on the part of the investigators. After the contract is completed, the DCT expects to have information about the need for a BRM acquisition/distribu-

tion system. Dr. Horwitz moved to approve the contract concept.

Dr. Goodman seconded the motion. The motion was approved unanimously.

Phase I/II Clinical Evaluation of Biological Response Modifiers for the Treatment of Cancer: Proposed resource contract recompetition; period of three years; estimated first year award of \$2 million. Because of potential conflicts of interest, Drs. Bolognesi, DiSaia, Marks, Phillips and Hellman left the room. Dr. Hellman requested that Dr. Elion serve as chairperson. Dr. Oldham stated that this contract was a renewal of a concept originally conceived by the Board in late 1979 to establish a mechanism for doing clinical trials with BRMs. The mechanism selected three years ago was the quick reaction task order contract awarded to contractors competitively selected from 27 institutions which successfully competed for a master agreement. The original concept was approved for five years, but money was only made available for three years. Dr. Oldham pointed out that a master agreement was an unfunded instrument; it simply was a key to compete for task orders. He indicated that another reason for the recompetition of this contract was that the DCT anticipated an increase in the number of institutions with the expertise and capability of performing these trials. The original concept allowance was for \$2 million per year as a ceiling. The funding was not held fixed at \$2 million each year but at an average of \$2 million a year over the period of time approved. In FY 80, \$2,558,658 was spent but only \$14,000 was spent in FY 81 under this master agreement mechanism. About \$1.2 million was spent in FY 82. Dr. Oldham reported that two thymosins, leucocyte and lymphoblastoid interferons, one immunomodulator and a variety of monoclonal antibodies had been tested during these contract periods. He predicted

that over the next few years further trials would include a variety of lymphokines, monoclonal antibodies and certain interferons.

Dr. Oldham stated that, for the recompetition, institutions will demonstrate their capability for three mock task orders. One is for macrophage activating factor (lymphokine); another is for an antimelanoma monoclonal antibody; and the third is for immune interferon.

Dr. Gertrude Elion asked whether the 27 institutions currently on the master agreement could recompile for the procurement. Dr. Oldham replied that everyone has an equal opportunity, and those holding current master agreements would have to recompile. Dr. Horwitz asked how many of the 27 institutions obtained task orders during the first contract period. Dr. Oldham replied that 15 different institutions were used; and three or four had two task orders. Dr. Elion asked if there was a limit to the number of institutions on the new agreement. Dr. Oldham stated that he expected a higher number of successful bidders than before, but there would be no upper limit established a priori.

Dr. Cooper inquired how decisions were made regarding the testing of biologics. Dr. Oldham explained that the initial selection process was done by a Decision Network Committee based on program recommendations and in concert with a number of consultants. He indicated that once the experimental concept was developed and the appropriate BRM formulation was available, two approaches were taken to design the clinical trial. One approach was to allow the task order responders to specify an experimental protocol in their proposals. The other approach was to permit the BRMP and the Decision Network Committee to dictate a very rigorous design. Dr. Oldham implied that in actual practice a combined approach was utilized.

He noted that the master agreement was a very flexible instrument, since it can theoretically handle trials as small as 15 patients or as large as 300 or 400 patients.

Dr. Horwitz asked if Dr. Oldham was satisfied with the master agreement mechanism. Dr. Oldham explained that, although there was room for improvement, it provided more flexibility and cost-effectiveness for the concept than other contract or grant mechanisms.

Dr. Cooper asked if there were any in vivo systems for testing BRM agents in animals. Dr. Oldham replied that the primate system was one possibility for certain BRMs, but he added that some lymphokines are active in man and not in primates. Dr. Calabresi asked how many BRMs had been tested to date and what percentage of these were satisfactory trials. Dr. Oldham replied that the BRMP had studied two thymosin preparations, about four interferon preparations, an immunomodulator called MVE-2 and one monoclonal antibody. Dr. Oldham indicated that he believed the investigators have done a reasonable job on all of them, and valuable data were gathered. He added that some institutions did better testing and garnered better data than others and that these institutions should have a better background of experience when the master agreement is up for recompetition.

Dr. Calabresi asked if Dr. Oldham had any specific recommendations to improve the contract. For example, should the Decision Network Committee develop the protocols rather than seek the participation of the contractors. Dr. Oldham thought the process worked best if the program staff set up the task orders. He explained that the Decision Network Committee was utilized primarily for advice; they help determine which BRMs

to put on trial and when to start those trials. He felt the process would improve if the insight obtained over the past three years was used in the recompetition. He stated that the requirements in the new RFP have been tightened. The new RFP will seek only institutions that have documented published capability in running BRM trials and laboratory assays. Dr. Leventhal asked if an institution was required to demonstrate proficiency in all three areas defined in the mock task orders or was one area of expertise sufficient for selection. Dr. Oldham replied that if the institution was experienced in one area and adequate in the others it would receive consideration.

Dr. Chabner suggested that Dr. Oldham explain or distribute literature on the organization, funding and decision-making process of the Decision Network Committee to the Board and also keep the Board informed on an ongoing basis about what goes on at committee meetings. Dr. Oldham agreed to provide some of that information during the lymphokine presentation he was to give the next day.

Dr. Calabresi then moved for concept approval; the motion was seconded by Dr. Elkind. The motion was approved without dissent.

Synthesis and Testing of Radiosensitizing Agents: Proposed recompetition of resource contract; period of three years; first year award of \$800,000. Dr. Pistenmaa indicated that one of the major problems in radiotherapy was the presence of radioresistant hypoxic cells in tumors which were probably the primary cause of the failure to eradicate these tumors by radiation therapy. A most promising way to overcome this resistance was to use radiosensitizing agents in conjunction with radiation therapy. The concept for the recompetition of this contract was the continuation

of a five-year program dedicated to the rational design and synthesis of novel or new radiosensitizers. The purpose of the new contract was to continue the directed synthesis of radiosensitizers and the testing program that has had five successful years of performance.

Dr. Pistenmaa noted that the initial goal of the first contract was to design a less toxic nitroimidazole radiosensitizers, compounds that would not enter neural tissue as quickly as misonidazole. He stated that about 180 compounds were synthesized by the contractor. A somewhat larger number were donated or were acquired by Dr. Ven Narayanan and his staff of the Drug Synthesis and Chemistry Branch of the Developmental Therapeutics Program, through the efforts of the Radiosensitizer, Radioprotector Analog Committee or the Radiosensitizer, Radioprotector Working Group. Almost 400 compounds were screened in vitro, and 73 compounds were tested in vivo, primarily in mice. Out of the 400 compounds, several appeared less toxic and had some radiosensitizing effectiveness. One, compound SR 2508, was approved this month by the FDA for Phase I clinical trials. Dr. Pistenmaa added that in addition to its radiosensitizing activity, SR 2508 was also a better chemosensitizer than misonidazole. This is a potential bonus of the program to develop radiosensitizers.

Dr. Pistenmaa explained that the goal of the next contract period is to seek other classes of compounds (without the nitro group) as electron-affinic radiosensitizers, since non-nitro compounds may be less toxic. Dr. Pistenmaa noted that the only current grant support in radiosensitizer research was a small effort at Tulane University. The investigator was trying to attach sugars and other compounds to nitroimidazoles

to improve their radiosensitizer effectiveness.

Dr. Racker asked how one could develop new compounds when the mode of action of nitroimidazoles was not well understood. Dr. Narayanan, the project officer, replied that the nitro group has a negative specific electron reduction potential (minus 385 millivolts) which removes electrons from macromolecules in hypoxic cells. Dr. Theodore Phillips added that, by withdrawing electrons, free radicals are created which probably cause irreparable DNA breaks.

Dr. Goldie asked if there was any evidence that strategies based the sensitization-of-hypoxic-cells theory had actually shown clinical benefits. Dr. Phillips, chairman of the RTOG Radiosensitizer Clinical Trials Committee, replied that trials with hyperbaric oxygen, which were based on the same theory, had been positive in cancers of the head and neck and of the cervix. These trials were conducted in Great Britain. Dr. Phillips also reported that there have been several studies with misonidazole that have demonstrated small gains.

Dr. David Bragg then moved for concept approval; the motion was seconded and approved.

BOARD OF SCIENTIFIC COUNSELORS  
DIVISION OF CANCER TREATMENT

Day 2 - January 28, 1983

VII. ANALYSIS OF STUDY SECTION REVIEW - DR. SAUL SCHEPARTZ

Dr. Schepartz presented background information on the scoring methods used for study section reviews and pointed out the continuing problem of variations in priority scores assigned by the study sections. The NIH instituted a system some years ago that normalized R01 scores. About two years ago, however, the decision was made to return to the raw score.

Dr. Schepartz then presented some priority scoring data from 1979 to 1983, broken down by study section. He underscored the fact that the approval rate varied from about 50 to 85 percent of grant applications over a four-year period. Similarly, the median priority score fluctuated from year to year and was lowest in 1981 (about 220) and highest in 1979 (about 285). He further noted that the priority scores were gradually decreasing, particularly since the raw score was reinstated.

To illustrate variations among study sections that review cancer grants, Dr. Schepartz called the Board's attention to the median scores given by Experimental Immunology (210) and by Experimental Therapeutics (255-260) for the October 1982 round. He suggested that the observed difference of 40 to 50 points between the two study sections was significant. Observing that score differences among study sections tended to be smaller in recent years, Dr. Leventhal remarked that it would be interesting to see a formal mathematical analysis of this trend. Dr. Schepartz

Dr. Schepartz said that he was not sure if any group is doing any quantitative study of those issues. Dr. Hellman pointed to the difficulty of doing a quantitative study because of the current concept of grant approval, where such approval is not synonymous to funding. Dr. Chabner remarked that the key issue is how many applications which study sections would like to see funded do not get funded. He suggested that program directors could obtain this information by observing study section proceedings.

Dr. Calabresi suggested four possible categories of proposals: 1) those of high priority with unanimous approval; 2) those of good priority are approved; 3) those of relatively lower priority that would be funded only if there were sufficient funds available; and 4) those that are clearly of poor quality and should be disapproved. He indicated that category two is where the study section should concentrate, because that is where the cutoff will come. Proposals could be assigned to each category initially. Then time should be spent fine tuning the priorities in category two.

Dr. Chabner pointed out that most good study section chairmen do recognize those distinctions and do focus on the grants in category two. He added that much of the discussion relates to the function of Study Sections and the management of the Division of Research Grants which are beyond the purview of DCT.

#### VIII. UPDATE ON LYMPHOKINES - DR. ROBERT OLDHAM

Dr. Oldham introduced his presentation by emphasizing the complexity and difficulty of identifying and deciding which lymphokines should be processed through the decision network system for advancement to clinical

trials. Dr. Oldham defined a lymphokine as a product of a lymphoid cell or a product that acted on lymphoid cells. He explained that the more general term often used was cytokine, a biological molecule that has activity on any biological system. Regardless of definition, Dr. Oldham reported there were a huge number of biological molecules that were active. Cytokines that the DCT was interested in have activities related to the immune system and deal with protective mechanisms in the area of cancer biology. He indicated that, for each cell system, there were multiple lymphokines that may affect cell proliferation, may suppress activities or may initiate activities. He noted that lymphokines and cytokines were active at every stage of cellular differentiation, and the interrelationships were not just on a per cell basis but between the different cell systems at different stages of differentiation.

Dr. Oldham stressed that each lymphokine can have multiple mechanisms of action. He reported that changing one or two amino acids in genetically engineered interferon, for example, can change the biological activity quite markedly.

Dr. Oldham noted that the historical approach of trying to produce lymphokines by stimulating human cells and isolating the active fractions from the cell supernatant had not worked very well. He indicated that a strategy that might yield more lymphokines entailed looking for lymphokines in cell lines. He reported that investigators examining B-lymphoid cell lines from patients with lymphoproliferative disorders had found that these cells sometimes produced high concentration of selected lymphokines. Lymphokines like migration inhibition factor, osteoclast activating factor and lymphotoxin were also produced by cell lines derived from patients with

lymphoproliferative disorders. Normal cell lines derived from individuals without a neoplasm, also produce a variety of lymphokines. Dr. Oldham reported that the best mechanism to obtain large enough quantities of pure lymphokine for clinical trials is to isolate the gene from the cell and produce the lymphokine by genetic engineering with microorganisms. Dr. Oldham predicted that 20 to 40 highly purified lymphokines will become available during the next five years.

Dr. Oldham indicated that certain lymphokines have some specific restrictions placed on their activity by the major histocompatibility complex (MHC) and only work on target cells with a particular antigenic complex. Within the class of specific lymphokines restricted by MHC were helper factors, suppressor factors and factors acting on macrophages. He stated that there were also less specific lymphokines and others that are non-specific and non-restricted. Dr. Oldham stressed that these factors were important considerations when planning clinical trial testing with a lymphokine.

Dr. Oldham then presented some of the preliminary results of clinical trials with interferon. He presented data that recombinant alpha interferon produced objective responses in patients with mycosis fungoides lesions. In a clinical study performed at the Frederick Cancer Research Center, the Clinical Center and the Naval Medical Center, 9 of 12 patients with drug resistant nodular lymphomas, chronic lymphocytic leukemias (CLL) and mycosis fungoides had shown partial responses when treated with recombinant alpha interferon. He pointed out that it was important to understand that although lymphokines were natural products, they are not necessarily non-toxic. He predicted that each preparation will have its own side effects.

Dr. Oldham also indicated that alpha interferon has anti-tumor activity in non-Hodgkins lymphoma, in renal cancer and CLL. He reported that some evidence existed for activity in breast cancer, in Kaposi's sarcoma and in some papillomas.

Dr. Oldham hoped that colony stimulating factor, interleukin-I and II and some of the cytotoxic factors of macrophages will become available for clinical trials within the next couple of years.

Dr. Oldham pointed out that BRMP's current pre-clinical screening program does not have a capability of testing lymphokine specificity. He added that many lymphokines were active in cells down the phylogenetic scale, as well as in human cells.

Dr. Oldham concluded his remarks by indicating that the BRMP was prepared to present a concept for Board approval at the next Board meeting for a contract, under a master agreement task order arrangement, through which the DCT can identify, procure and make lymphokines available for clinical trials.

#### SYNOPSIS OF DISCUSSION

Dr. Marks commented that a candid appraisal of the costly experience with interferons should come before concept review of clinical trials with lymphokines was initiated. He requested to have an expert evaluation of interferon's anticancer activity relative to traditional agents before proceeding with new BRM trials. He also asked if there was a useful pre-clinical screen available for evaluating potential biologic agents. Dr. Oldham replied that there was no simple way to evaluate lymphokines in a pre-clinical setting for prediction of clinical activity. For

example, genetically engineered immune interferon can promote macrophage activation, colony stimulation activity and T-cell proliferation.

Dr. Marks suggested that a pre-clinical screen could entail a battery of assays.

Dr. Racker asked if it was necessary to purify lymphokines by classical means before the genetic approach was used to manufacture larger quantities. Dr. Oldham replied that there is evidence that the genetic message can be cloned out of activated cells without isolating the protein products. He also agreed that a critical review of the interferon trials was warranted.

Dr. Elkind asked if there was any mechanism in place to deactivate clinical interest in a particular lymphokine. Dr. Oldham answered that there was presently no way of deactivating interest until predictive tests for clinical activity were complete. He indicated that decisions made to proceed with clinical trials were based on analogous activity in animal models and on in vitro evidence.

Dr. Bolognesi asked how interferon ranked compared to other chemicals that had antitumor activity. Dr. Oldham replied that interferon was one of the more active new agents tested in the last several years. He reported that in Phase I testing interferon has fared as well as most chemotherapeutic agents and, perhaps, just below the level of cis-platin, adriamycin, VP-16 and some of the stronger alkylating agents.

Dr. Cooper asked Dr. Oldham to present at the next Board meeting, a priority plan for lymphokines, their availability and proposed testing combinations. Dr. Oldham replied that such a plan was problematic because BRMs are different than the classical cytotoxic drugs. Dr. Oldham noted

that progress in the BRMP is currently dependent on the availability of purified lymphokines and would remain so for the next couple of years. He estimated that it would require a gigantic budget for the the DCT to take an active role in developing new lymphokines.

Dr. DiSaia felt that the Board would not obtain an adequate assessment of the clinical activity of interferon by next June because it was used primarily in chemotherapy resistant patients. He recommended that the Board wait for the results of the Phase I/II trials before judging their efficacy. Dr. Racker requested that Dr. Oldham present the Board with a plan of future BRMP priorities. Dr. Oldham agreed that would be a good starting point for the next Board meeting.

Dr. Leventhal agreed with Dr. DiSaia that there was evidence that interferon was active in papillomatous disorders. She disagreed that it was too early for a progress report on interferons, because a number of abstracts had been written for last year's Cancer meetings and again for this year's meeting. She felt that a discussion of these data on interferons would be very useful to the Board in planning future trials with all biologic agents.

Dr. Chabner and Dr. Hellman summarized the major points brought out during the discussion.

- There was a need for preclinical screening assays for BRMs.
- Availability of a BRM should not be the sole determinant of the decision to test it in patients.
- An assessment of the interferon trials would be useful before proceeding with other clinical trials.
- A developmental plan should precede a concept review of any new activities.

Dr. Bolognesi requested that the Board also discuss the progress made with monoclonal antibodies. Dr. Oldham indicated that such discussion would be profitable since there were about 50-100 patients treated with monoclonal antibodies throughout the United States for therapeutic efficacy.

Dr. Oldham noted that the BRMP's current activities had emanated from specific recommendations of the Board's BRM Subcommittee which were made two years ago. He noted that the subcommittee had recommended Phase I and II trials of interferon, thymosin, MVE 2, and BCG. Dr. Oldham added that experiments with tumor necrosis factor were proceeding satisfactorily. He predicted that active immunization with tumor antigens will not start until monoclonal antibodies fully define the tumor antigens. He reported that the BRMP was in the process of evaluating at least two member of each of three interferon classes--leukocyte, fibroblast, and immune--for activity as BRMs in at least one Phase I and/or Phase II trial. Thus the major recommendations of the BRM Subcommittee have been pursued.

Dr. Oldham then presented a diagram of the process of developing a BRM from conception to general medical practice. He noted that it was very similar to the flow diagram used for drugs. The sequence is:

- Biological activity determination
- Formulation and purity testing
- Toxicologic investigation
- Phase I clinical trials
- Phase II clinical trials
- Phase III clinical trials and/or use in combination treatments

He indicated that the interferons were in the midst of Phase II clinical trials.

Dr. Oldham announced that the BRMP has a contract planned that will provide a data base on BRMs of interest; that is, it will catalogue the physical and biological properties of hundreds of biologicals that are of interest to the Decision Network Committee and the BRMP.

Dr. Oldham indicated that information on each particular BRM is presented to the Decision Network Committee. Questions of purification, biological evaluation, formulation, procurement and scale-up are then addressed by the Decision Network Committee prior to deciding whether or not it was possible, probable and reasonable to proceed to toxicology, Investigational New Drug (IND) application, Phase I trials and finally Phase II trials.

Dr. Oldham explained that the Decision Network Committee (DNC) was composed of NCI members, scientists from the BRMP and other NIH institutes, and consultants from universities and industry, on a rotating basis. He reported that the DNC evaluated the progression of BRMs; made decisions on the progression of particular agents; recommended procurement; recommended assays, Phase I trials, and Phase II trials; recommended program interactions; and recommended workshops and briefings. Dr. Oldham added that there was an Operating Committee, which basically operated like a steering committee of the DNC.

Dr. Oldham then described the workings of the DNC by giving a hypothetical example. If a company sent the BRMP macrophage activating factor (MAF) for evaluation and a literature package, the review of MAF's biological activity would be presented to the DNC. The BRMP would

then proceed according to their advice. He noted that the DNC met monthly and that there was also a retreat process where consultants were utilized. Dr. Hellman stated that the Board would like additional information on the ongoing decisions of the DNC and how they were implemented.

IX. ACQUISITION OF COMPOUNDS FOR SCREENING - DR. JOHN DRISCOLL

Dr. Driscoll stated that the objective of the Developmental Therapeutics Program's (DTP) Drug Development Program was the discovery and development of new clinically useful anti-cancer drugs. Its goal, in concert with the DCT clinical trials mechanism, was the introduction of approximately six new agents into Phase I clinical trials each year. He explained that the DTP's Drug Development Program was organized into drug discovery and preclinical development components. Each of these areas consumed roughly 50 percent of the \$34 million extramural contract budget. The preclinical development component carried out the work needed to move a material into clinical trial, for those compounds discovered in the Program, as well as those discovered at other institutions. This included responsibility for the pharmaceutical manufacture of the clinical dosage forms used in NCI sponsored clinical trials.

Dr. Driscoll indicated that he would restrict his remarks to the drug discovery component which was further divided into new lead discovery and lead improvement (analog development) activities. The emphasis of the DTP in drug discovery is on new lead discovery. Dr. Driscoll stated that a new lead could evolve from basic research discoveries. He pointed out that the goal of the new National Cooperative Drug Discovery Group is to accelerate the transfer of basic science into rational drug discovery

and new clinical agents. Pharmaceutical companies often adequately cover analog development for compounds on which they have a patent position. He indicated that the relationship between the Drug Development Program and Industry was complementary and collaborative. More than 300 companies have signed commercial discreet agreements with the DCT for the preclinical antitumor evaluation of their compounds.

Dr. Driscoll defined a new lead as the first compound of a series discovered to have therapeutic activity. An analog is a structural modification of the lead compound, prepared in an attempt to improve the activity, or other pharmacologic properties of the lead.

Dr. Driscoll then presented some examples of new leads and analogs. He noted that daunorubicin was isolated as a new lead from a fermentation screening program. Adriamycin, a structural analog of daunorubicin, was discovered in a planned program of lead development, using mutated forms of the microorganism which produces daunorubicin. Cis-platinum was a serendipitously discovered new lead. However, the NCI has screened over 1200 platinum analogs in a search for an improved drug. CBDCA was chosen for clinical trial by the NCI based on preclinical antitumor activity and extensive toxicity testing with dogs and rodents. Anthracenedione was a lead discovered in the NCI Screening Program. He indicated that anthracenedione had been quickly improved through synthetic modification to produce the congener (analog) mitoxantrone.

Dr. Driscoll noted that there were two major variables in any screening program, biological screening models and the selection of compounds chosen for testing. He stated that tumor models used by DTP were considered to be the most appropriate available. Tumor model improvement, however,

was an area of applied research, which underwent continuous development in the DTP program. The dynamic nature of this area was exemplified by the stem-cell assay, in vitro/in vivo tumor correlation studies, the development of metastatic tumor models and DTP's search to find models for drug resistance. He stated, therefore, that his presentation would deal only with the compound selection process.

Dr. Driscoll then presented a general schematic of the compound selection process. He indicated that it is not a random process but is very selective. The acquisition contractor is required to supply the NCI with more than 20,000 structures which the NCI has not screened previously. To do this, a computer program initially identifies the duplicates and then the structures of the resulting 20,000 new compounds are analyzed by two additional computer programs. One program rates the structural uniqueness of each compound relative to all of the compounds that were previously tested. The other program is specially designed to predict in vivo P388 leukemia prescreen activity based on the structural characteristics of previously tested compounds. The resulting data are then analyzed by doctoral-level medicinal chemists at NCI, who make the final selection of the 10,000 compounds that are screened annually in the murine P388 leukemia assay. Emphasis is placed on the uniqueness of the structure.

Dr. Driscoll reviewed the typical productivity of the screening program. He indicated that about 10,000 compounds enter the in vivo prescreen and approximately five percent, or 500 of these compounds, would be active against this tumor system. About half of these active compounds are then chosen based on structural uniqueness and are further evaluated in a panel of tumors. Out of this screening, he estimated that

approximately 20 compounds that had activity high enough in one or more of these tumor panel models, would be designated as compounds for Decision Network review, (DN2A) in the linear array drug flow diagram. These are then presented to the DTP's Decision Network Committee with approximately 8 to 10 potential candidates being approved for clinical trial each year following toxicology testing. To illustrate the productivity of the DTP Screening Program, Dr. Driscoll discussed compounds in 1) the DTP Prescreen, 2) the Tumor Panel, 3) preclinical development and 4) IND submission stage.

Dr. Driscoll reported that 87 percent of the compounds tested in any given year were obtained as the result of a request by the DCT or its contractors (active acquisition). He noted that active acquisition methods contributed 91 percent of the compounds entering the tumor panel with the acquisition contractor contributing a total of 61 percent. Active acquisition accounted for 77 percent of the compounds currently in preclinical development, and 69 percent of the compounds which were submitted for Investigational New Drug (IND) applications during the past six years. Dr. Driscoll reported that the contribution of the acquisition contractor ranged from 60 percent of the P388 pre-screen actives to 15 percent of the INDA submissions during the most recent six-year period. The reduction can be explained by the significantly higher probability of synthesizing an analog which will achieve clinical trial status, than discovery of a completely new structural entity. Historically, voluntary (non-contract) contributors have emphasized analog development.

Dr. Driscoll indicated that new leads account for 19 of 33, or 58 percent, of the IND applications which the DCT filed during the past six years. The five compounds attributed to the acquisition contractor all

fall into the new lead category. These compounds are levamisole, deoxycoformycin, mitoxantrone, acodazole and tiazofurin. Of the 10 voluntary submissions, four came from the DCT intramural program. These compounds include AZQ, ketotrexate (5-methyltetrahydrohomofolate), dihydro-5-azacytidine and spiromustine. Of the remaining 6 compounds, DON and N-methylformamide had been submitted so long ago that it was difficult to trace their history. Spirogermanium, bisanthrene, mercaptopurine (MP) and amasacrine were voluntary submissions.

DTP active acquisition efforts, when combined with intramural contributions, accounted for 100 percent of the 14 analogs for which IND applications were filed over the past six years.

Dr. Driscoll then summarized NCI's role in the discovery and evaluation of anticancer drugs that have achieved commercial (NDA) status. He reported that at least half of the 32 commercially available compounds were discovered prior to the inception of the NCI Drug Development Program in 1955. Since the inception of the program, the NCI has played a discovery role in 8 of 16 of the commercially available anticancer drugs. He noted that the NCI has played a major role in the clinical evaluation of all 16 compounds.

Dr. Driscoll cited examples of anticancer drugs which have resulted from leads discovered in the screening program. These include the nitrosoureas (BCNU, CCNU, MeCCNU, and PCNU), dacarbazine (DTIC), AZQ, mitoxantrone and tiazofurin.

The nitrosoureas were based on methyl-nitrosoguanidine, a lead that was discovered in the NCI Screening Program. DTIC, like the nitrosoureas, was discovered at the Southern Research Institute under an NCI synthesis

and screening contract. PCNU was a structurally improved nitrosourea also prepared at Southern Research Institute. Mitoxantrone, a promising clinical agent in late Phase II clinical trial which appears to have a spectrum of activity similar to adriamycin without a number of the anthracycline toxicities, was a rationally designed improvement over its parent. The parent compound was a DTP screening discovery from the Allied Chemical Corporation. The drug design improvement which followed was made at at Midwest Research Institute, an NCI synthesis contractor

In his summary Dr. Driscoll stressed that there currently was no viable alternative to the DCT selective acquisition and screening process for discovery of new anticancer drug leads. He pointed out that, thus far, non-screening approaches, such as rational drug design, have had a minimal impact on the recent discovery of new anticancer agents.

#### SYNOPSIS OF DISCUSSION

Dr. Hellman commented that he was gratified to learn that mitoxantrone had emerged as an active agent, particularly since the Washington Post had published a sensational report that patients had been given "ballpoint ink" as an antitumor agent.

Referring to the attribution of drug discoveries, Dr. Goldie pointed out that Dr. Robert Noble and Charles Bier first isolated and identified vincristine and vinblastine, although Eli Lilly may have first recognized their antitumor activity.

Dr. Hellman asked the Board for comments on Dr. Driscoll's presentation. There were no comments, and discussion led to other related topics.

Dr. Hellman reported that he had received a letter from

Dr. William Powers of the NCAB, expressing his concern with the possible utilization of the stem cell assay. Dr. Robert Shoemaker, the Section Head in charge of the In Vitro Section in the Drug Evaluation Branch, was then called upon to brief the Board on progress made in developing the stem cell assay. He reported that the current contract was designed for determining if the clonogenic assay could be used as a compound screen and not for predicting the activity of a drug in a given patient. Based on two years of research, he felt that it was feasible to conduct screening with six tumor types: breast, colorectal, kidney, lung, melanoma and ovary. In terms of screen validity, a majority of standard agents were detected in the assay and non-toxic compounds were negative in the system. A blind test of 50 known compounds, made to test reproducibility within and among laboratories, resulted in a correlation coefficient of about 0.8. Dr. Shoemaker reported that 67 out of 77 unknowns screened, which were negative in the P388 pre-screen, also were negative in the clonogenic assay. One of the ten active compounds was a novel structure and may represent a new lead.

Dr. Driscoll reminded the Board that it had approved the rebudgeting of DTP funds into a model development program called In Vivo/In Vitro Correlations. This money will fund experiments trying to correlate the activity of anticancer drugs in the in vitro stem cell assay with the activity of these agents against human xenografts grown in nude mice.

Dr. Chabner stated that he was quite encouraged with the indication that the assays may have identified some unique compounds. He also reviewed some of the problems with its use as a clinical predictive assay including the problem of metabolic activation, the rescue of drugs by nutrients

in the medium, and the low cloning efficiency.

Dr. Chabner mentioned that the results of the first three years of the stem cell assay contract was scheduled for review at the June Board meeting and will give the Board an opportunity to assess the success of the experiments.

Dr. Cooper asked if the reason that the rate of discovery of new drugs has not appreciably changed since the establishment of the NCI program was due to the fact that it is getting tougher to find new drugs.

Dr. Driscoll agreed with this assessment, indicating that the alkylating agents and antimetabolites were rapidly identified as active anticancer agents in the early years of the cancer program. Dr. Schepartz added that it now takes considerably longer to develop a drug for the market than it did in the early 1950s.

Dr. Goodman stated that he was concerned about the low productivity of the R01 grants in the screening process. Dr. Driscoll replied that the basic objective of the R01 grants was different than the contract mechanism and there is no requirement for R01 grantees to submit compounds to DCT for testing. Only about two percent of the compounds screened by the DCT came from NCI grantees. He noted that Dr. Moreshwar Nadkarni, Chief of Extramural Research/Resources Branch, was very aggressive in trying to get grantees to submit compounds. He sends them a letter requesting information on compounds they promised to submit in their grant applications.

X. COMBINED HORMONAL THERAPY WITH AN LHRH AGONIST AND AN ANTIANDROGEN  
IN PROSTATIC CANCER - PROFESSOR FERNAND LABRIE

Dr. Chabner introduced Dr. Labrie, Professor of Medicine at the University of Laval in Quebec and an expert in the field of molecular endocrinology.

Dr. Labrie began his lecture by explaining that luteinizing hormone-releasing hormone (LHRH) is a 10 amino acid peptide hormone produced in the hypothalamus and controls the secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) in the anterior pituitary gland. It was discovered in 1971 by Andrew Schally. He indicated that LHRH was released in a pulsating manner, approximately once every 60 minutes. He noted that, if this natural peptide was modified by changing the terminal glycine moiety to ethylamide and replacing the leucine in position six with D-leucine, the activity of the peptide was increased 200 to 500 fold. However, male rats treated with the LHRH analog experienced a 50 percent reduction in the size of the secondary sex organs and in the size of the testes.

Dr. Labrie explained the possible mechanism of action behind this observation. The LHRH agonist acts on the pituitary to release a large amount of LH. When the excess LH reaches the testes there is a loss of LH receptors which, in turn, decreases the synthesis of androgens in the Leydig cells. Treatment with the LHRH agonist blocks the enzymes at two steps in the biosynthesis of testosterone. In effect, medical castration was achieved by using the LHRH agonist. Dr. Labrie also indicated that sperm formation was also blocked.

Dr. Labrie stated that, in man, LHRH inhibited the secretion of male hormones by 90 to 95 percent, but it took 5 to 12 days before maximum

inhibition was achieved. He indicated that this event was, unfortunately, preceded by a period of male hormone stimulation regardless of the dose or route of LHRH administration. In cancer patients, this stimulation of male hormones was accompanied by a flare-up of disease and pain in 20 to 25 per percent of the cases. Dr. Labrie reported that antitumor response was achieved in 74 percent of the cases by administration of LHRH agonist alone, comparable to the effect observed using high doses of estrogen or surgical castration. Given alone, LHRH agonist may also cause a slight but transient circadian stimulation of androgens. To prevent these adverse effects he had used a combined treatment of LHRH agonist with a pure anti-androgen. The anti-androgen blocks the entry or effect of the male hormones by binding to the androgen receptors in the cancer cells. Dr. Labrie noted that the anti-androgen was normally given one day before the LHRH agonist, to prevent the side effect of transient androgen stimulation obtained with LHRH agonist alone.

Dr. Labrie observed by bone scan significant reductions in bone metastases in patients treated with both LHRH agonist and the anti-androgen. In patients not previously treated, a response was observed in 100 percent of the patients. Combined therapy markedly decreased testosterone levels and blocked the formation of precursors, such as dehydroepiandrosterone. In addition, there was an average of 60 percent decrease in blood acid phosphatase activity. Cortisol secretion was not affected.

Dr. Labrie then discussed what happens physiologically after castration. The concentration of androgens in the blood is reduced by approximately by 90 percent. However, the residual 10 percent of the total androgens in the body are produced by the adrenals and exert 40 percent

of the maximal effect on the tissues. Since prostate cancer was hormone dependent, this residual effect explained why only 30 percent remission was observed in castrated patients instead of the 100 percent found in patients receiving combined therapy.

Dr. Labrie reported that the results obtained in castrated patients that had been given the LHRH agonist/antiandrogen combination after previous hormone therapy were not as good as when the combination was given as primary therapy. He explained this on the basis of selection of hormone independent clones. He emphasized that the percentage of remissions was also higher using combined therapy initially than when using castration or estrogen treatment exclusively. Dr. Labrie concluded that it was important to institute combined treatment as early as possible when the tumor cells are androgen dependent and the chance of therapeutic success is greater.

#### SYNOPSIS OF DISCUSSION

Dr. Bolognesi asked why some experiments using adrenalectomy for treatment of prostate cancer reported negative results. Dr. Labrie clarified that castration had often been performed before adrenalectomy. Dr. Portlock asked how many of the patients treated had measurable lesions, especially soft tissue masses. Dr. Labrie replied that only 10 percent of the patients had soft tissue masses but that almost all of the patients had measurable bone lesions.

Dr. David Pistenmaa asked what effect the combination of LHRH agonist and anti-androgen had on sexual function of patients. Dr. Labrie explained that a decrease in libido occurred in almost all the patients, although

some patients continued to be sexually active.

Dr. Samuel Wells asked what was the mean follow-up period for all of the patients. Dr. Labrie replied that they ranged from 3 or 4 to 11 months. Dr. Wells also wanted to know what percentage of the patients had a partial response. Dr. Labrie answered that all of the responses had to be considered partial because of the difficulty associated with documenting complete responses in bone. Dr. Wells asked if Dr. Labrie had experimented with other tumors such as breast cancer. Dr. Labrie indicated that he had no experience with breast cancer.

Dr. Byer asked if combined LHRH agonist-antiandrogen therapy was superior to using castration and antiandrogen initially. Dr. Labrie replied that, although both therapy strategies were equally good, castration should produce maximal inhibition of testosterone biosynthesis. Dr. Calabresi speculated that the combined therapy regimen might select for cancer cells that are non-androgen responsive by killing off the cells that were androgen dependent. Dr. Labrie expected that this was not the case, if therapy was performed early enough, because the combined therapy might minimize cell division and reduce the probability of selection of hormone-resistant cells. Dr. Calabresi asked if there were any other clinical trials confirming these findings. Dr. Labrie answered that some were planned in the United States and Europe in the near future.

Dr. Chabner commented that the National Prostate Cooperative Group was now interested in doing a very similar trial to the one that Dr. Labrie conducted at Laval. Dr. Chabner pledged his support of this research if the NCAB gives the DCT responsibility for it.

XI. NEW BUSINESS

Dr. Calabresi proposed that the Board sponsor a workshop to explore new methodology in clinical trials. Dr. Chabner noted that he received a letter from Dr. Robert Temple at the FDA requesting a meeting with the DCT on this subject. He told Dr. Temple that he would delay his response until a permanent Director was appointed for the Cancer Therapy Evaluation Program (CTEP). He indicated that the time was now appropriate to have this meeting. Dr. Wittes indicated that he had met with Dr. Simon and developed a tentative agenda for such a workshop. Dr. Calabresi suggested that it was important to immediately follow up on the initiative generated by yesterday's meeting.

Dr. Hellman then discussed the site visit schedule.

- April 1983, Surgery Branch, Clinical Oncology Program, Dr. DiSaia Chairman, report to the Board in June 1983.
- October 1983, Navy Medical Center Medical Oncology Branch, Dr. Calabresi Chairman
- February 1984, Laboratory of Medicinal Chemistry and Biology, Dr. Horwitz Chairman.
- February 1984, Clinical Pharmacology Branch, Dr. Goldman Chairman
- June 1984, Biologic Response Modifier Program, Dr. Cooper Chairman.

Thereupon, the meeting was adjourned at 2:10 p.m.

NATIONAL INSTITUTES OF HEALTH  
NATIONAL CANCER INSTITUTE  
DIVISION OF CANCER TREATMENT  
BETHESDA, MARYLAND

BOARD OF SCIENTIFIC COUNSELORS

January 27-28, 1983

Bethesda Marriott

AGENDA

Thursday, January 27

8:30 a.m.                      Opening Remarks                      Dr. Samuel Hellman

Welcome Board members, Dr. Vincent DeVita,  
Director, National Cancer Program, and National  
Cancer Institute.

Announcement: We also welcome members of the public  
who are with us today. Those of you who may wish  
to express views regarding any items to be discussed  
may do so by writing to the Executive Secretary of  
the Board within ten days after the meeting. Any  
statement by members of the public will receive  
careful consideration.

PROCEDURE FOR CONDUCT OF MEETINGS

- (a) Informal, vote by voice. A show of hands when not unanimous.
- (b) Board members are reminded that material furnished for review purposes and discussion during the closed portion of the meeting is considered privileged information. Advisors and consultants serving as members of public advisory committees may not participate in situations in which any violation of conflict of interest laws and regulations may occur.
- (c) To avoid conflict of interest, apparent or possible, members shall absent themselves from the meeting when an application of proposal submitted by his/her own institution is being discussed. In the case of higher education institutions or other similar systems where the multiple campuses are geographically separated, the term "own institution" must be interpreted to mean the entire system in which the member is an employee, consultant, officer, director, or trustee, or in which he has a financial interest. This definition is extended a step further to include, in the case of state higher education systems, those persons who are employees of, or consultants to, any component of the entire system of state government. For example, State Department of Health.

\*Telephone for messages: 301/496-6161

Thursday, January 27, 1983

8:30 a.m.	I. Chairman's Remarks	Dr. Samuel Hellman
8:45 a.m.	II. NCI Director's Report	Dr. Vincent DeVita
9:15 a.m.	III. DCT Director's Report	Dr. Bruce Chabner
10:15 a.m.	INTERMISSION	
10:45 a.m.	IV. Report of SORDs Committee	Dr. Phillip DiSaia
12:00 noon	LUNCH	
1:00 p.m.	V. Observational Studies and Randomized Trials	Dr. Alvan Feinstein Dr. Charles Moertel Dr. Emil Freireich Dr. Richard Simon
3:00 p.m.	INTERMISSION	
3:30 p.m.	VI. Concept Review	Dr. Bruce Chabner/ Associate Directors
5:00 p.m.	ADJOURNMENT	

Friday, January 28

8:30 a.m.	VII. Analysis of Study Section Review	Dr. Saul Schepartz
9:30 a.m.	VIII. Update on Lymphokines	Dr. Robert Oldham
10:15 a.m.	INTERMISSION	
10:45 a.m.	IX. Acquisition of Compounds for Screening	Dr. John Driscoll
12:00 noon	LUNCH	
1:00 p.m.	X. Combined Hormonal Therapy with an LHRH Agonist and an Antiandrogen in Prostatic Cancer	Prof. Fernand Labrie Univ. of Laval
2:30 p.m.	ADJOURNMENT	

The first part of the document discusses the importance of maintaining accurate records of all transactions. It emphasizes that proper record-keeping is essential for the company's financial health and for providing reliable information to stakeholders. The document then outlines the specific procedures for recording transactions, including the use of standardized forms and the requirement for double-checking entries.

The second part of the document addresses the issue of data security. It highlights the risks associated with unauthorized access to sensitive information and provides guidelines for ensuring the confidentiality and integrity of the data. This includes implementing strong password policies, using secure communication channels, and regularly updating security software.

The third part of the document focuses on the training and development of staff. It stresses the need for ongoing education to ensure that employees are equipped with the latest skills and knowledge required for their roles. The document outlines a structured training program that includes both on-the-job training and formal classroom instruction.

The final part of the document provides a summary of the key points discussed and offers recommendations for future actions. It encourages a culture of continuous improvement and invites feedback from all employees to help refine the processes and policies outlined in the document.

## APPENDIX



# EXHIBIT I

## Pre-SORDS Committee Meeting

Date: January 26, 1983, 10 AM

Place: Building 31, Room 3A47

### Members Present:

Dr. Phillip J. DiSaia, Chairman  
Dr. Ernest V. deMoss, NCI Liaison  
Ms. Susan Hubbard, NCI  
Dr. Walter Lawrence  
Dr. Steven A. Rosenberg, NCI  
Dr. William W. Shingleton

### Guests Present:

Dr. Bruce Chabner, Director, DCT  
Dr. Daniel Hoth, Acting Associate Director, CTEP  
Dr. Edwin Jacobs, Acting Branch Chief, CIB  
Ms. Kim Horgan, Administrative Officer, CTEP

### CTEP and Development of Surgical Oncology

The meeting was called to clarify the relationships among the SORDS Committee, the Surgery Section, CIB; and the DCT. This seemed desirable as SORDS has interest in training surgical oncologists and in development of departments (Divisions, Sections) of surgical oncology in academic centers where training and research may be conducted. Training and resource development are generally not functions of DCT; hence the need for exploring these relationships and for discussing mechanisms to implement what SORDS has perceived as important goals in the development of surgical oncology.

Dr. DiSaia pointed out the success of the radiotherapists in developing training and research facilities. Trying to explore the means by which these objectives had been reached a decade or more ago did not seem productive at this time, nor applicable to the problem at hand in the views of several participants.

Dr. Jacobs pointed out that the function of CTEP was to identify areas of scientific interest and to encourage research in these areas usually through the cooperative agreement or grant mechanism. Dr. Jacobs noted too that policy change and means of bringing about large shifts in fund allocation to facilitate development of surgical oncology training and research centers were beyond the role of CTEP.

Dr. Rosenberg objected that the best interests of surgical oncology could not be served by specific project development (as studies in melanoma recently developed by surgeons mentioned by Dr. Jacobs). He noted that surgery differed from medicine as there were few pure surgical problems. There is no surgical science per se; hence the scientific approach focused narrowly on pure surgical problems in cancer research is not likely to be fruitful and will not forward the development of research for surgical oncologists.

Dr. Lawrence agreed that outlining specific research projects would not achieve the desired goals. What is needed first, both Rosenberg and Lawrence agreed, is more training for young surgeons in the clinical and laboratory aspects of cancer research and more places for conducting such research.

Dr. Rosenberg summarized by noting that the only way to go was the allocation of large sums of money to departments of surgical oncology. He estimated the infusion of 3 to 5 hundred thousand dollars into 20 institutions for 5 years would be necessary to develop the number of surgical oncologists who could compete successfully for grant money.

Dr. DiSaia noted that these matters had been discussed many times before. The critical question was what mechanism could be used to help develop surgical oncology.

Dr. Lawrence pointed out that an affirmative action approach to help surgical oncology would not be acceptable to BSC. He noted too that the RFA which resulted in funding of 5 P20 planning grants fell short of the goals for greater expansion of surgical oncology, and felt that reissuing the RFA is important.

#### DCT and the Development of Surgical Oncology

Dr. Chabner was present during the last half of the meeting. He outlined the organizational relationship of the Surgery Section to CIB, to CTEP and to DCT. While the Surgery Section, having approximately 3 million dollars in funded grants in its portfolio was thought to be too small to become an "activity" on recent review by the Executive Committee, NCI, Dr. Chabner felt that this decision should be reconsidered when the item is returned to the Executive Committee. He noted that the Surgery Section was 16th out of 19 cancer activities in dollar size of its portfolio.

As Dr. Chabner was not present during earlier discussion, Dr. DiSaia recapitulated the previous discussion about the perceived needs for developing surgical oncology. He noted that 20 institutions should be funded with one

quarter to a half million dollars for 3 to 5 years. Realizing that any such recommendation would have to go through the Board of Scientific Counselors for concept review, he queried; How do we do it? and What is the mechanism? Is the P20 grant still a viable way?

Dr. Chabner felt that the impact of the five funded P20 grants should be evaluated before making any further decisions about this matter. After this survey of existing P20 grants he felt that SORDS could go back to BSC with a request for another RFA for P20 grants. He said he doubted that the BSC would accept the idea of funding 20 surgical oncology centers.

Drs. Lawrence and DiSaia expressed doubt about the value of an appraisal of the present P20 grants as so little time has elapsed, less than a year since funding. In summary, Dr. Chabner suggested first evaluating the present P20 grants. If staff feels that they are positively fulfilling a need, then a request for reissuing an RFA may be presented to BSC in June.

In response to a question by Dr. Rosenberg about the mechanism for getting money to centers for surgical oncology, Dr. Hoth noted the government could not fund money without competition.

#### Clinical Education Grants

Dr. Chabner mentioned the use of this grant as another possible mechanism for helping surgeons. Dr. Lawrence, having some experience with this type of grant in the past, opined that it wouldn't help surgical programs, and added surgical oncologists need laboratory as well as clinical training. Dr. Chabner noted that there was a need for training as well as support for the department of surgical oncology. Dr. Shingleton noted that the grant was concerned mainly with cancer epidemiology, nutrition and prevention. Dr. Chabner felt that it would be appropriate to look into surgical oncology as a target area, paying postgraduate (as well as undergraduate) trainees, and evaluate the grant for reissuance of an announcement. Dr. Chabner said later that it was important to encourage student interest by exposing them to the concepts of surgical oncology during medical school.

Dr. Chabner noted again that DCT would supplement DRCCA funds if necessary to target at least 8 Physician Investigator Development Awards for surgeons with acceptable applications in the first round of funding this year.

#### Names for Board of Scientific Counselors

In response to a request for names of surgeons as candidates for BSC, the following names were suggested:

1. William L. Donegan, M.D., Medical College of Wisconsin  
Milwaukee, Wisconsin

2. Yeu-Tsu N. Lee, M.D., University of Southern California, Los Angeles, California
3. Barrie Anderson, M.D., University of Iowa, Iowa City, Iowa.
4. Peter J. Mozden, M.D., Boston University, Boston, Mass.
5. Rodrique Mortel, M.D., Hershey Medical School, Hershey, Pa.
6. Edward D. Holyoke, M.D., Roswell Park, Buffalo, N.Y.
7. Donald Skinner, University of Southern California, Los Angeles, California.

This ad hoc committee was adjourned around noon sine die.

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Ernest V. deMoss, M.D., M.P.H.

## EXHIBIT II

### MINUTES OF THE SORDS COMMITTEE MEETING

Date and Time: January 26, 1983, 1-4:30 PM

Place: Building 31, Conference Room 9

Present:

Philip J. DiSaia, M.D. (Chairman)  
Ernest V. deMoss, M.D., M.P.H. (NCI Liaison)  
Dani P. Bolognesi, M.D.  
Jerome J. DeCosse, M.D., Ph.D.  
William L. Donegan, M.D.  
John Durant, M.D.  
Bimal C. Ghosh, M.D.  
E. Carmack Holmes, M.D.  
Ms. Susan Hubbard  
Walter Lawrence, Jr., M.D.  
Eugene N. Myers, M.D.  
Theodore V. Phillips, M.D.  
Stephen A. Rosenberg, M.D., Ph.D.  
William W. Shingleton, M.D.  
Samuel A. Wells, M.D.

Absent:

Barry D. Kahan, M.D.  
Richard E. Wilson, M.D.

Guests:

Bruce A. Chabner, M.D.  
Robert E. Wittes, M.D.  
Edwin M. Jacobs, M.D.  
Daniel Hoth, M.D.  
S. Stephen Schiaffino, M.D.

Summary of Morning Meeting, January 26, 1983

Dr. DiSaia summarized the proceedings of the morning meeting (see Pre-SORDS Meeting Minutes, January 26, 1983). He emphasized that what was really needed was a structured plan that would be acceptable to the Board of Scientific Counselors and that could be operationalized within NCI.

RO1 Review, Experimental Therapeutics Study Section and Dr. Schiaffino

Dr. S. Stephen Schiaffino, Deputy Director, DRG, was introduced and questioned about discontinuance of the Special Surgical Study Section (SSS) and review of RO1 grants in surgical oncology. Dr. Schiaffino noted that there was not much activity in the SSS and that it had been incorporated into the Experimental Therapeutics (E.T.) Study Section whose Executive Secretary is Dr. Ira Kline. Dr. Schiaffino continued that because of the present size of E.T., it would be divided into two subdivisions which would include a pre-clinical section and a clinical section. The latter section would review surgical oncology grants. In order to accommodate surgical oncology grants, he would like to have a roster of surgeons who would be willing to serve on the study section. This change in organization of E.T. will require a change in charter, addition of members and revision of the guidelines. Dr. deMoss will monitor the progress of these changes and develop the roster of surgeons to serve on E.T. Subcommittee members were asked to submit lists of names to Dr. deMoss.

In response to general concern about limited success for approval of clinical grant applications, Dr. Schiaffino noted that in contrast to laboratory research, clinical research entailed bigger problems with more variables and hence fewer approvals. This point was illustrated by a handout entitled "Submission, Approval and Mean Priority Scores of Competing RO1 Applications of MD's and PhD's for Council Years 1976-1981." Based on 75,611 applications during the years under consideration, this report showed approval rates of 73% and 74% for M.D.'s and Ph.D.'s respectively in projects with no human subjects, and approval rates of 64% and 61% in projects with human subjects (See handout). Dr. Schiaffino also made available a document "Analysis of the Initial Review of NIH Grant Applications to Conduct entitled Clinical Research," August 1982, prepared by the Research Analysis and Evaluation Branch, DRG (See handout), a publication of much greater detail. It was not discussed. Dr. Schiaffino noted that there would be a paper in the journal, Clinical Research, about this subject in the near future. In response to a question about proper review for surgical oncology applications, Dr. Schiaffino pointed out the need for cooperation between the program director and the study section executive secretary in identifying appropriate regular and ad hoc committee members.

Dr. Chabner and a Variety of Issues

a. The "Physician Investigator Development Award" guidelines were reviewed briefly by Dr. Chabner, who said that DCT was very supportive of this program and would supplement funds of DRCCA as necessary to see that 8 positions are funded for surgery applicants provided that there are 8 meritorious applications approved by the study section. It was noted that Dr. deMoss would attend the review sessions for these applications and would work with Dr. Barney Lepovetsky, Chief, Research Manpower Branch, DRCCA, in developing a roster of surgical specialists and subspecialists as candidates to serve on the review committee.

b. The status of Surgical Oncology becoming recognized as a program "activity" was discussed by Dr. Chabner, who noted that the Executive Committee NCI, had rejected the change in November 1982. At that time, the Surgery Section Portfolio was three million dollars, a size considered inadequate to become an "activity." It was noted that another three million in surgery projects could be found included in P01 grants but this could not be broken out for the Surgery Section Portfolio. Dr. Chabner pointed out that of 19 other cancer "activities" surgery would rank 16th in size. Feeling that surgery should not be turned down on size alone, he will bring the matter back to the Executive Committee. In response to Dr. DiSaia's question about how becoming an "activity" would be helpful, Dr. Chabner said that it would give the Surgery Section greater identity for referral of surgical grant applications and related questions. (In this regard specific referral guidelines would be developed).

c. "Clinical Education Grants" were discussed as a mechanism for encouraging greater medical student interest and improved teaching in surgical oncology. Dr. Chabner pointed out that these grants were for faculty support and curriculum development for cancer activities and teaching at an undergraduate level, and in the past have included support for house staff personnel who are engaged in medical student training. Dr. deMoss will look into adding surgery as a target area in the grant guidelines.

d. Issuance of another RFA for P20 Grants for development of departments of surgical oncology was discussed by Dr. Chabner who felt that any further action should be postponed until the June BSC meeting. Prior to that meeting he felt that the five present P20 grants should be surveyed to document what kind of programs have been developed, who is being trained and how the money is being used. Dr. deMoss will look into this matter.

In regard to reissuance of the RFA, which requires an amount of money set aside by DCT, Dr. Chabner said that centers for surgical oncology research must be based on people doing competitive research. He emphasized that the BSC will oppose "giving away money" to people who are not doing excellent research.

e. Drs. Lawrence and Bolognesi suggested revision of the R01 and P01 program announcements. Dr. Chabner said that this may have to wait until the June BSC meeting if extensive changes were made. However, Ms. Hubbard noted that minor revisions may be made without additional approval. In this regard, Drs. DeCosse and Shingleton emphasized the need to broaden the guidelines to include areas of surgical oncology research other than therapy.

Miscellaneous Discussion

a. Dr. Robert E. Wittes, new Associate Director, CTEP was introduced. Dr. Wittes said that he had worked in collaborative studies for the past 10 years at Memorial Sloan-Kettering Institute in New York City and had a good appreciation of the role of surgeons in research. He said that CTEP was interested in the development of surgical oncology and that he would like to work with SORDS in furthering this end.

b. Dr. Myers said that Dr. Geza Jako, Otolaryngologist, and member of the National Cancer Advisory Board expressed an interest in setting up another subcommittee representing a task force for head and neck cancer as this field may not be receiving enough attention. It was pointed out by Dr. deMoss that the Head and Neck Contract Program (HNCP) was just being terminated and that CTEP was working with a group of HNCP investigators and others who are interested in forming a head and neck cancer study group. Protocols are being developed and CTEP will work with the group to explore means of continuing this activity.

c. Dr. DiSaia reviewed the day's deliberations in preparation for a presentation to the BSC the next day.

d. The meeting was adjourned until immediately after the next BSC meeting. Arrangements for the next SORDS meeting will be announced later.

Ernest V. deMoss, M.D., M.P.H.

## PRIORITIES FOR THE DIVISION OF CANCER TREATMENT

The Division of Cancer Treatment of the National Cancer Institute has as its purpose the discovery and development of curative treatment for malignancies. In October of 1982, facing fiscal year 1983, the Division and its constituency, the cancer research community, face difficult choices in a time of rapid scientific progress and shrinking real dollars. Never have there been so many deserving alternatives for treatment research, encompassing the wide range from biological factors to particle radiotherapy, from rationally designed drug regimens to bone marrow transplantation. The possibilities for success are real; prototype experiments have demonstrated the feasibility and potential effectiveness of these approaches, and yet hard choices must be made. The economic realities of 1983 have limited our ability to follow all paths. I would like to discuss these choices with you today and indicate what I believe to be the most important scientific priorities for DCT. I welcome your comments and advice.

Let me begin by discussing first the question of mechanisms of support, and then consider specific directions for scientific work. It is traditional at board meetings to discuss plans in terms of mechanisms. At least four mechanisms exist through which DCT supports treatment research: (1) investigator initiated research in the form of grants or cooperative agreements; (2) program-initiated procurement, or research and development, usually in the form of contracts; (3) intramural research; and (4) collaboration with private industry or private institutions, with various degrees of cost sharing. Investigator-initiated research (as conducted by grantees and by intramural scientists) has always been the highest priority of this Division, and will remain so until the majority of cancer patients can be cured by simple therapies. This priority is consistent with the need to discover new forms of treatment. However, the need to develop and test new treatments requires the use of other support mechanisms. Procurement, formulation, toxicology, and early clinical testing are most easily accomplished through contract support. A targeted program such as ours can only function if support for discovery is linked to a development system. Thus the contract and cooperative agreement mechanisms are essential to our mission. For the past three years, our grant and intramural programs have been able to survive and increase modestly only because of significant cuts in the NCI and DCT contracts programs. Further cuts in these contracts will in effect dismantle our development apparatus in the areas of drugs, radiotherapy, and biologicals. We must keep this fact in mind when we entertain further cuts in the contract efforts of DCT.

I would like to comment further on the relationship of DCT to private industry and private institutions. Collaborative research has existed between DCT and the private sector since the inception of the Cancer Chemotherapy National Service Center in the mid-1950's, primarily in the form of voluntary submission of compounds for testing by NCI and the licensing of NCI-discovered drugs by private pharmaceutical houses. This relationship is likely to become more important in the immediate future as public funds become more limited, and as the potential for profit in anticancer drugs increases. It is important for the NCI to actively encourage private firms to assume responsibility for candidate agents at earlier stages in drug development, and at the same time continue to make our drug screening and clinical testing apparatus available for compounds submitted by private firms. We must encourage private industry to participate in the over-all planning of drug and analog development. All these aspects of public-private cooperation are now taking place, and we hope will be further accelerated by the \$3 million National Drug Discovery Groups, which will encourage a liaison between public, academic, and private parties in the effort to discover new agents.

I would now like to turn to the problem of scientific priorities. The improvement of cancer therapy requires at least two major phases of research, each requiring its own mechanisms of support and presenting unique problems in terms of scientific priorities. These two phases are "discovery" and "development". I would like to discuss our priorities for each of the categories of research represented in DCT: drugs, biologics, radiologic modalities, and radiotherapeutics.

In the area of treatment discovery, our major source of new treatments for the past 2 decades has been the drug screening process. New drugs have been identified from compounds submitted from private sources and academia. On a smaller scale, we have procured plant and antibiotic compounds through contracts. I believe that, in the short term, drugs are still likely to be the most significant contributor to the improvement of cancer treatment. In the drug discovery area, we have two most important short-term objectives for our Division: The first is to integrate new developments in molecular biology and biochemistry into the process of drug design; this we will attempt to do through our National Drug Discovery Groups. The second is to develop more relevant systems for screening and identifying new compounds. This latter effort will require us to move toward screening systems which employ human tumors, drug-resistant tumors of relevant biochemical configuration (such as those which have pleiotropic resistance), and metastatic tumors. We have initiated efforts in each of these areas. It is my firm belief that the next substantial advances in cancer treatment will accompany these changes in screening.

It is worth noting that we are far from a solution to the problem of a human tumor screen. Our major hope, in vitro tumor cloning, has proven to be a difficult system to use for technical reasons. Improvement in this system will require a better understanding of growth requirements and regulation by cytokines before reliable in vitro human tumor screens will be available. I personally suspect that we will make greater progress through research which will identify the genetic or mutational basis of drug resistance; this information can then be used to set up relevant screening systems based on biochemical considerations.

In the last three years, the scope of our discovery activities has broadened considerably, with the addition of the biological response modifier program and the radiation research program which now comprise 10% and 22%, respectively, of our over-all budget. We are, in addition, beginning to strengthen our investment in surgical research.

In the longer run, biologicals must be regarded as having significant advantages (lesser toxicity, greater specificity, and possibly diversity) and this latter program must be supported effectively through its formative years. I feel that this support must primarily be in the form of grants, until sufficiently promising leads are discovered to warrant the extensive procurement and development systems currently in place for drugs. At present, 84% of BRMP funds are in investigator-initiated research, either intramural or extramural, and I feel this balance is appropriate. In the short-term, of all the biological leads, monoclonal antibodies have the most promise for making a significant clinical contribution to cancer diagnosis and treatment. This area clearly warrants highest priority for immediate development through contracts and program-initiated grants. Our recent RFPs in this area attest to the support we are providing for this work. I see a relative long-term growth in the BRMP budget as basic research progresses to the isolation and characterization of lymphokines, cytokines, and other growth-regulatory compounds, and as we develop a better understanding of their potential in antitumor therapy.

In radiotherapy, our highest priorities in the discovery phase are less well-defined; it is clear that we must support grant research into basic mechanisms of radiation damage. A number of important topics await further study: The enzymatic basis of resistance to radiotherapy, the effects of radio-modifiers (protectors and sensitizers), and the role of sulfhydryls in radiation damage. In addition, there are a number of important areas of developmental work in radiotherapy, particularly in the area of particle irradiation and diagnostic imaging, which require and are receiving contract or cooperative agreement support. I will return to these topics when I consider developmental priorities.

I would now like to turn to DCT priorities at the development end of the spectrum. In the development phase for new drugs, there are both administrative and scientific goals of great importance which must be addressed. Important short-term goals for drug development are (1) to develop better preclinical predictive systems for acute and chronic toxicity of new drugs, a subject we are actively exploring in our contract toxicology program; (2) to accelerate the process of Phase I testing in man (so that fewer patients are exposed at subtherapeutic doses), a subject under intense examination by a pharmacokinetic working group in DTP; and (3) to develop better predictive systems for choosing drugs for treating general classes of tumors, and for choosing treatment in individual patients. A broad spectrum of research projects in this area is ongoing in both the intramural and extramural communities, and includes work on refinement of the human tumor stem cell assay, as well as newer approaches such as analysis of tumor DNA for drug-resistance genes by transfection or with gene probes. All these activities will require contract or RFA support in the future.

For radiotherapy, the highest developmental priority is support of an effective clinical trial of neutron therapy (\$2.6 M), and secondly the establishment of a clinical network for evaluation of NMR as a diagnostic procedure (\$1.04 M). These efforts will serve as prototypes for the coordinated evaluation of major new modalities on a national scale, a major objective of RRP.

The final phase of development of new treatments is the clinical trials apparatus, primarily supported through program project grants and the cooperative group network. Program project grants are an essential element because they allow coordinated laboratory and clinical evaluation of new therapies. These grants now constitute \$60 M, or 22% of our budget, while the cooperative clinical trials groups have \$42 M in funding or 14% of our budget. While both mechanisms have been productive in the past, they are costly. The financial stringency in cancer research today requires a careful re-examination of both mechanisms to be sure that they remain viable and productive. I will discuss proposals to improve the quality of PO-1's in the director's report. In general, I see the need here for more careful development of grants both through investigator and NCI efforts in the planning stage, and a more critical eye in the funding process by the NCI so that funds are allocated only to those high-priority components of PO-1 grants. In the cooperative group program, our most immediate problems are to reduce duplication and improve coordination in clinical trials in specific diseases, and, secondly, to determine appropriate funding for our grantees. We have made significant progress through changes

in the review process. Important tasks remain in the cooperative group program. We need to:

1. Establish a reasonable balance between headquarters and member funding.
2. Improve the assignment of funding for new and re-competing grants to group members through greater input by DCT staff and by the group chairman.
3. Establish mechanisms for adjustment of funding of non-competing grants to allow for changes in accrual, performance, and productivity.

I want to discuss two other components of the DCT program which are absolutely essential to the success of this Division: the intramural program and the major extramural centers for cancer research. I believe that the NCI intramural program is a remarkable national resource with unique ability to attempt innovative and high-risk projects in a facility dedicated to cancer research. Certain programs must be streamlined in the immediate future: Consolidation is under way in the areas of preclinical pharmacology, biologics and immunology, and clinical oncology. Duplicative and nonproductive elements must be removed to make room for newer, high priority efforts: The study of drug resistance in human tumors, the development of monoclonal antibody-related diagnosis treatments, the coordination of clinical and laboratory investigations into the viral etiology of cancer and the biology of transformation. This latter point deserves particular emphasis since many laboratories at the NCI must now have human tumor material for research purposes.

Finally, the preservation of extramural centers of cancer research is a goal of high priority to this Division. Effective cancer research requires a critical mass of investigators. The bridges between basic and applied science, between laboratory and clinic have never been more important. We are committed to the proposition that the outstanding extramural program must remain viable as research institutions, particularly through preserving and strengthening of the PO-1 grant.

In conclusion, the considerable accomplishments of the past decade have provided us with a wealth of important new ideas and a therapeutic development-clinical trials apparatus for testing these ideas. Despite the increasingly severe fiscal constraints of the coming year, I expect that we will be able to support our high-priority projects, and expect that we will see exciting results in the near future.

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10/11/82

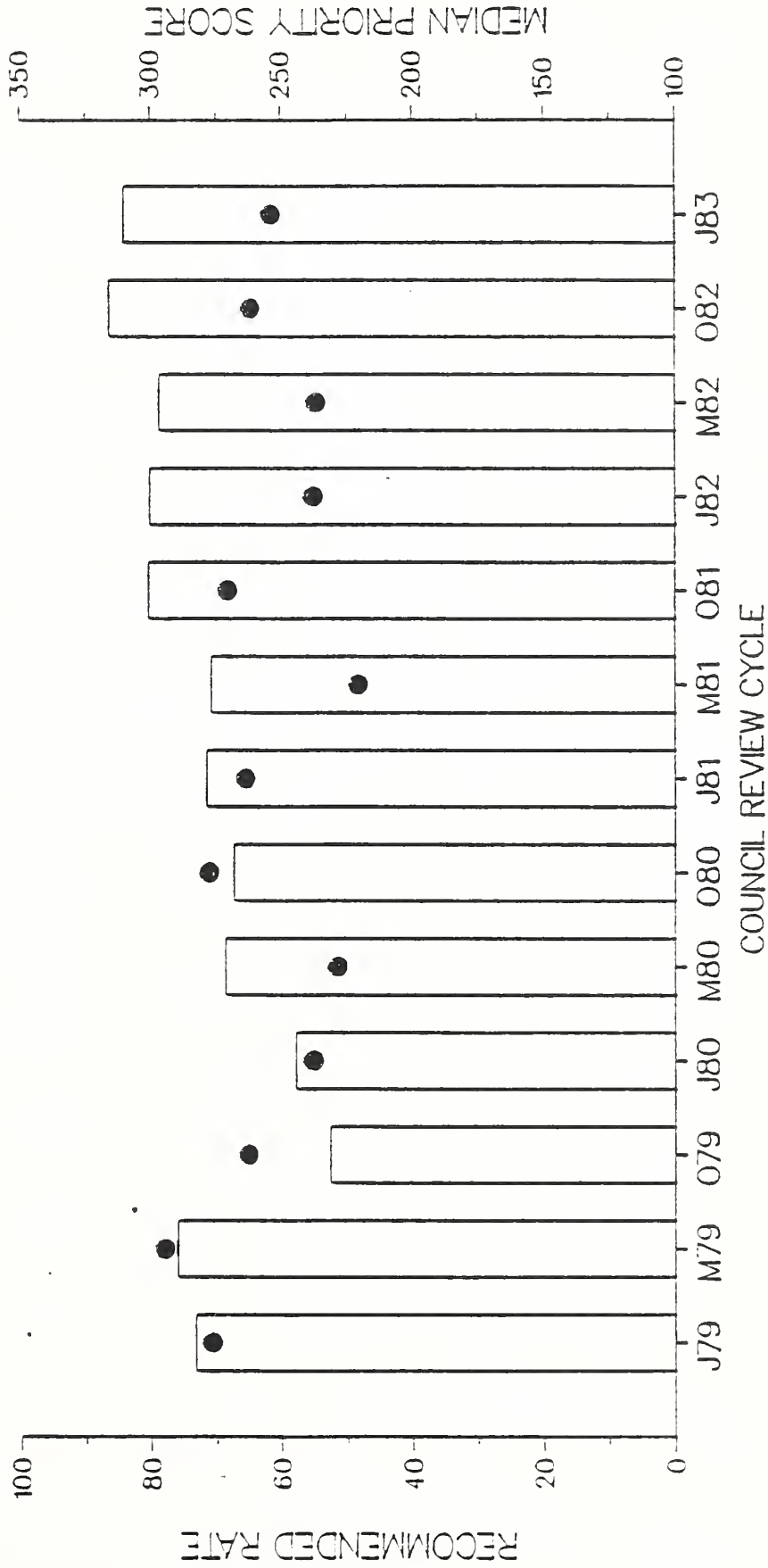
ANALYSIS OF STUDY SECTION REVIEW

BACKGROUND MATERIAL

# RECOMMENDED FOR APPROVAL RATES AND MEDIAN PRIORITY SCORE FOR RESEARCH PROJECTS JAN'79 - JAN'83

STUDY SECTION: CPA

(● = median priority score of approved applications)  
(bar = recommended rate)

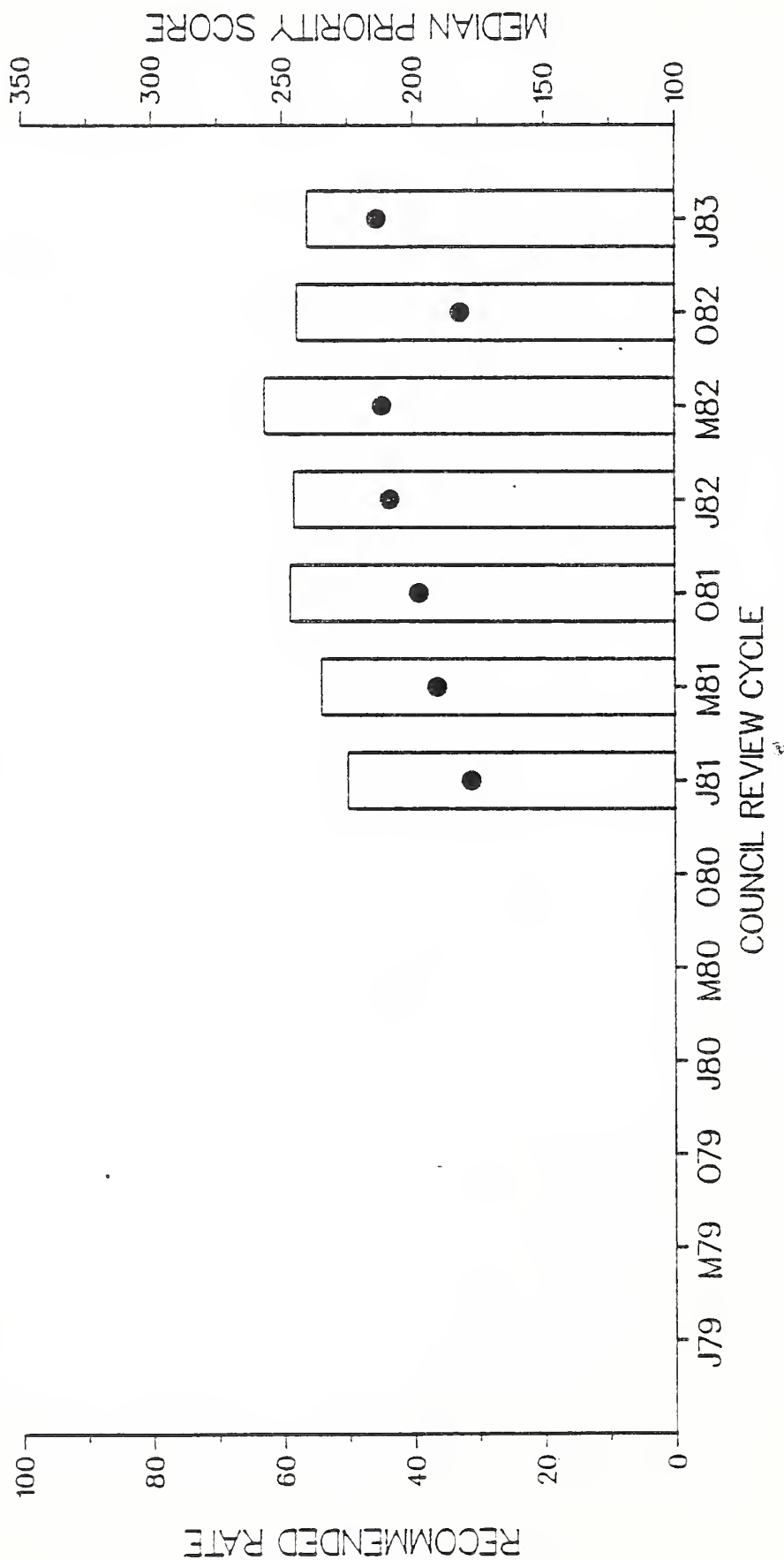


Rates are based on number of applications.  
Data are not shown if less than 10 applications were recommended for approval.  
Source: NIII/DRG/SAB

# RECOMMENDED FOR APPROVAL RATES AND MEDIAN PRIORITY SCORE FOR RESEARCH PROJECTS JAN'79 - JAN'83

## STUDY SECTION: EDC 1

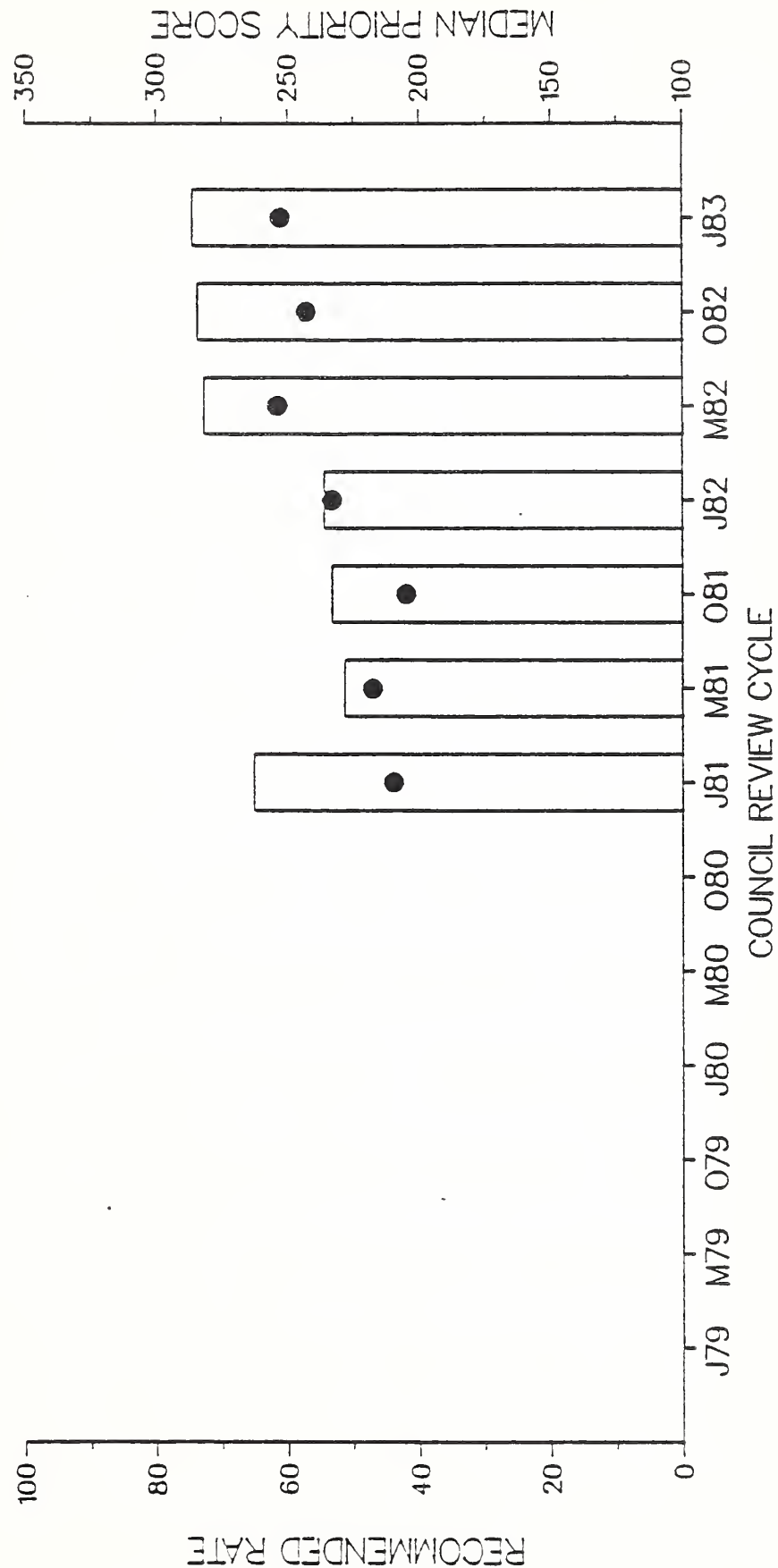
(● = median priority score of approved applications)  
(bar = recommended rate)



Rates are based on number of applications.  
Data are not shown if less than 10 applications were recommended for approval.  
Source: NIH/DRG/SAB

# RECOMMENDED FOR APPROVAL RATES AND MEDIAN PRIORITY SCORE FOR RESEARCH PROJECTS JAN'79 - JAN'83 STUDY SECTION: EDC 2

(● = median priority score of approved applications)  
 (bar = recommended rate)

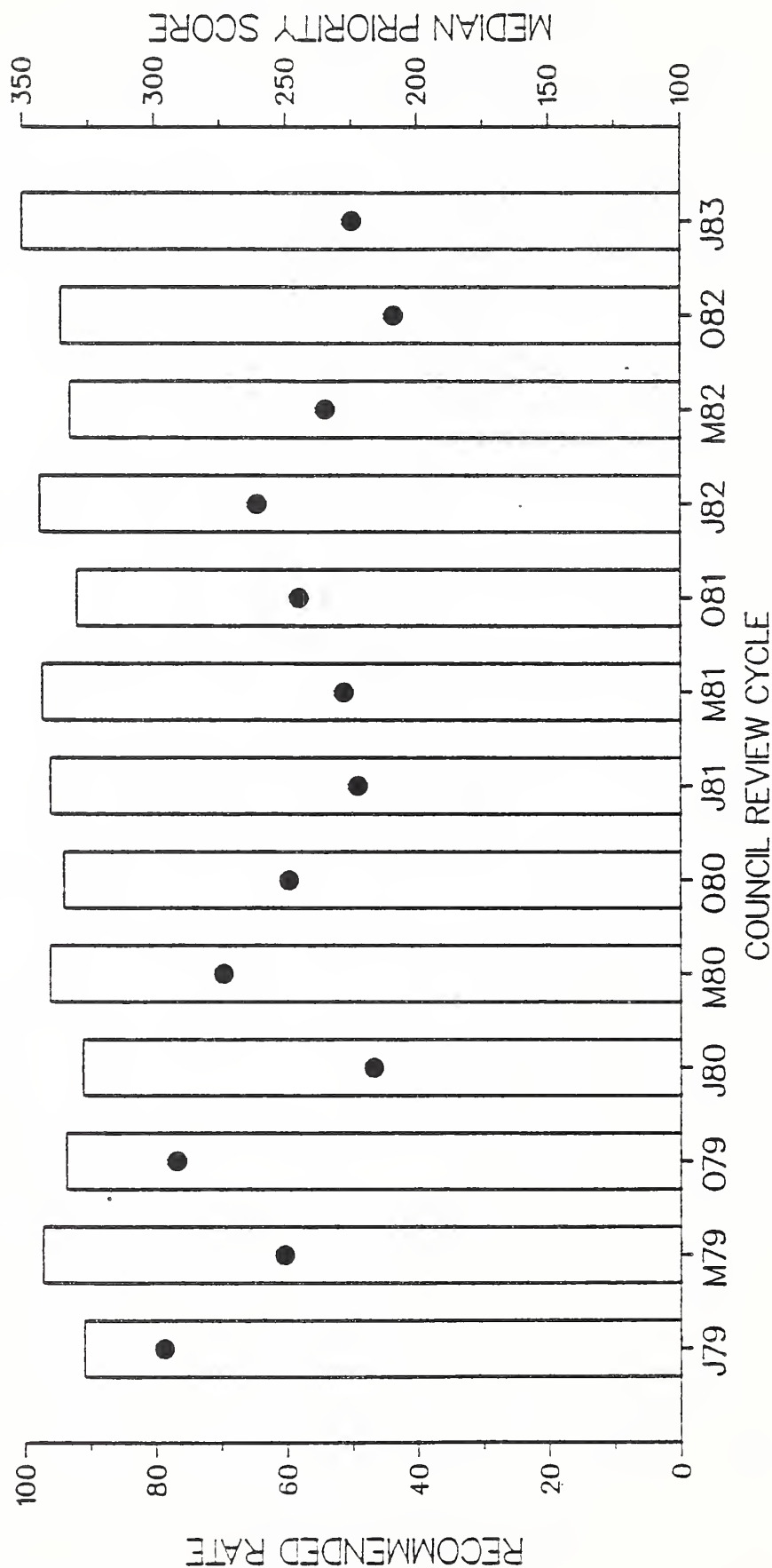


Rates are based on number of applications.  
 Data are not shown if less than 10 applications were recommended for approval.  
 Source: NIH/DRG/SAB

# RECOMMENDED FOR APPROVAL RATES AND MEDIAN PRIORITY SCORE FOR RESEARCH PROJECTS JAN'79 - JAN'83

## STUDY SECTION: EI

(bar = recommended rate)  
(● = median priority score of approved applications)

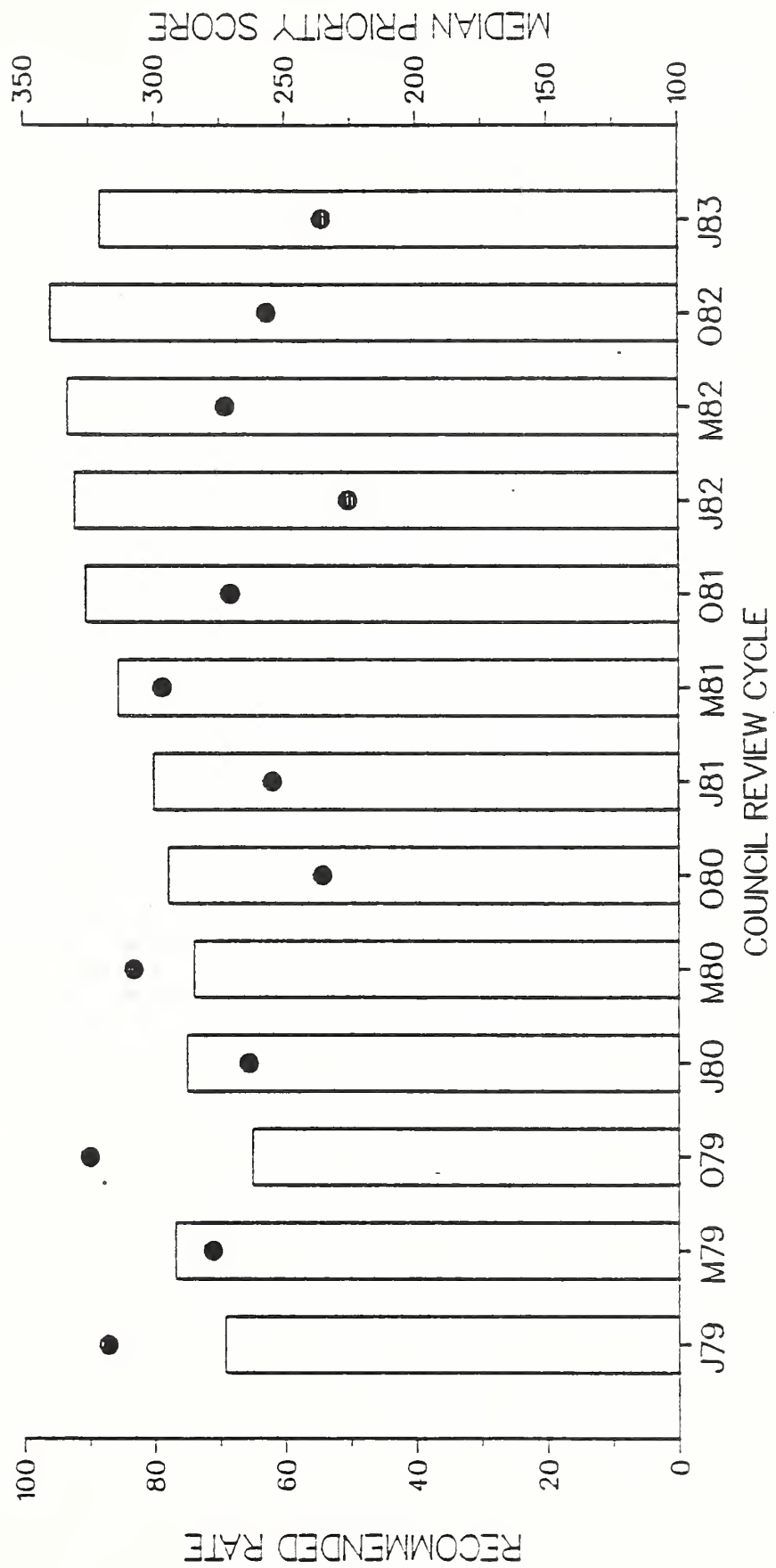


Rates are based on number of applications.  
Data are not shown if less than 10 applications were recommended for approval.  
Source: NHH/DRG/SAB

# RECOMMENDED FOR APPROVAL RATES AND MEDIAN PRIORITY SCORE FOR RESEARCH PROJECTS JAN'79 - JAN'83

## STUDY SECTION: ET

(● = median priority score of approved applications)  
(bar = recommended rate)

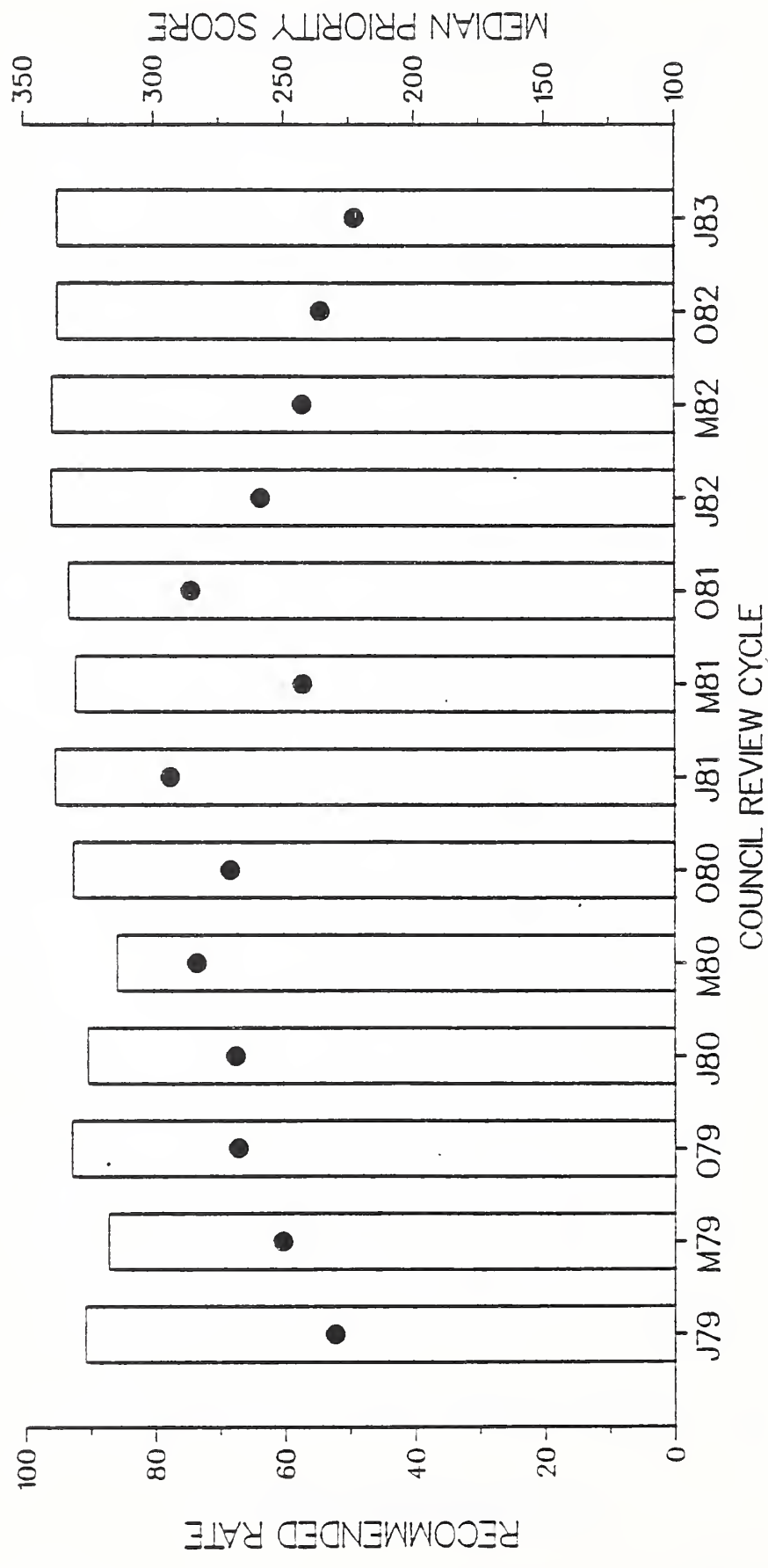


Rates are based on number of applications.  
Data are not shown if less than 10 applications were recommended for approval.  
Source: NII/DRG/SAB

CHART 4 - 12/13/82

# RECOMMENDED FOR APPROVAL RATES AND MEDIAN PRIORITY SCORE FOR RESEARCH PROJECTS JAN'79 -- JAN'83 STUDY SECTION: EVR

(● = median priority score of approved applications)  
 (bar = recommended rate)

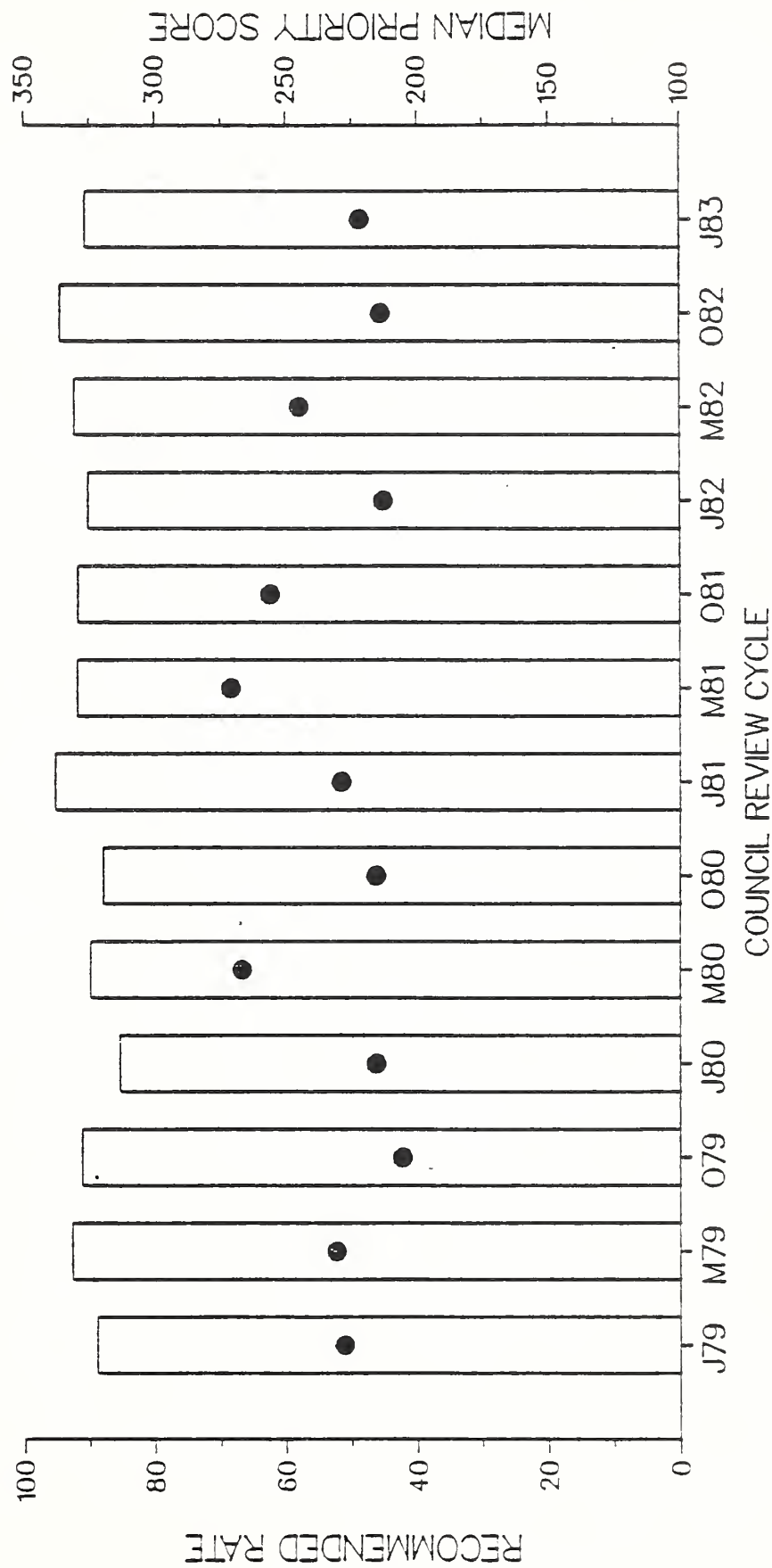


Rates are based on number of applications.  
 Data are not shown if less than 10 applications were recommended for approval.  
 Source: NIH/DRG/SAB

# RECOMMENDED FOR APPROVAL RATES AND MEDIAN PRIORITY SCORE FOR RESEARCH PROJECTS JAN'79 - JAN'83

STUDY SECTION: IMB

(● = median priority score of approved applications)  
(bar = recommended rate)

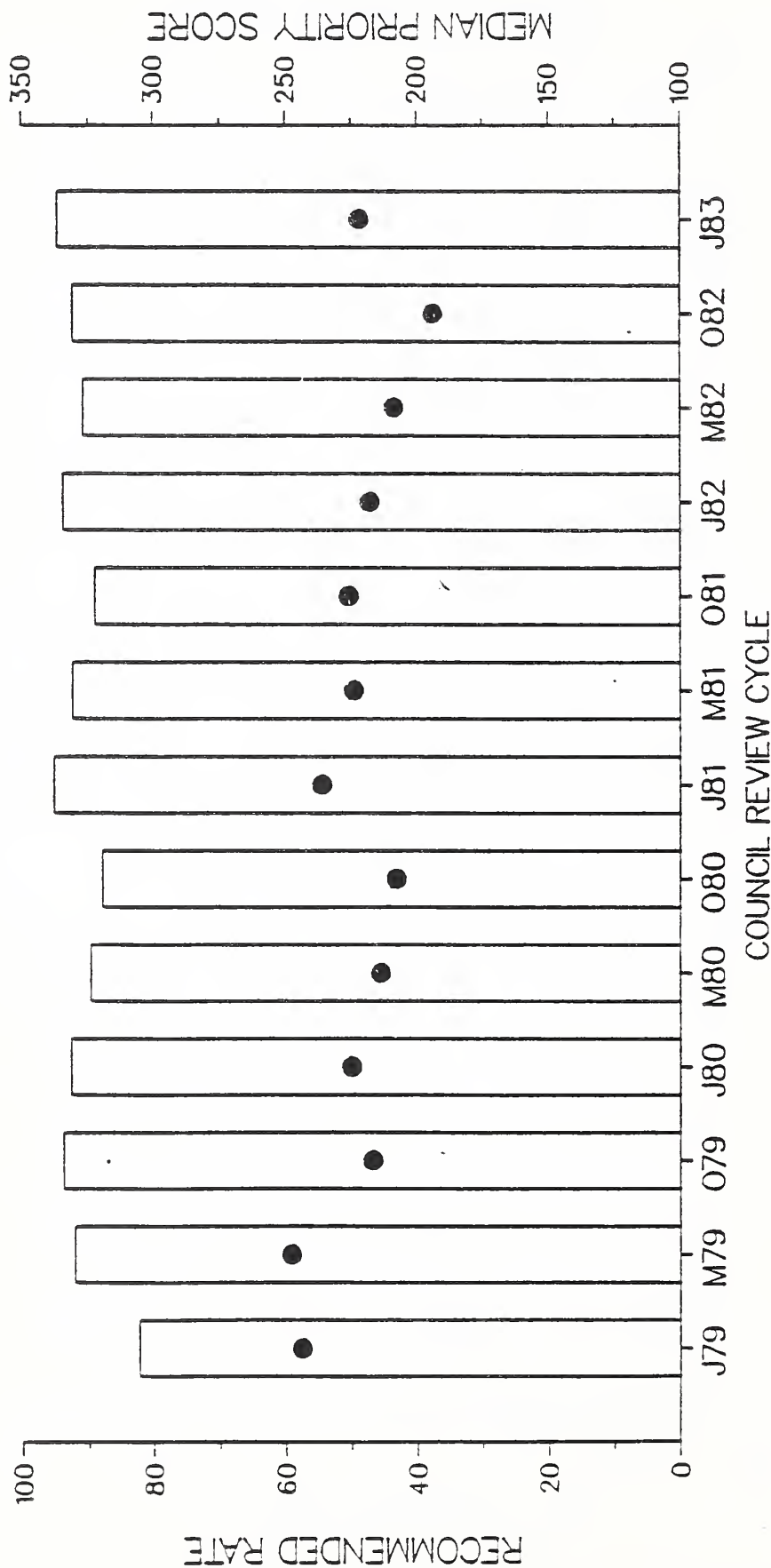


Rates are based on number of applications.  
Data are not shown if less than 10 applications were recommended for approval.  
Source: NII/DRG/SAB

# RECOMMENDED FOR APPROVAL RATES AND MEDIAN PRIORITY SCORE FOR RESEARCH PROJECTS JAN'79 -- JAN'83

STUDY SECTION: MGN

(● = median priority score of approved applications)  
(bar = recommended rate)

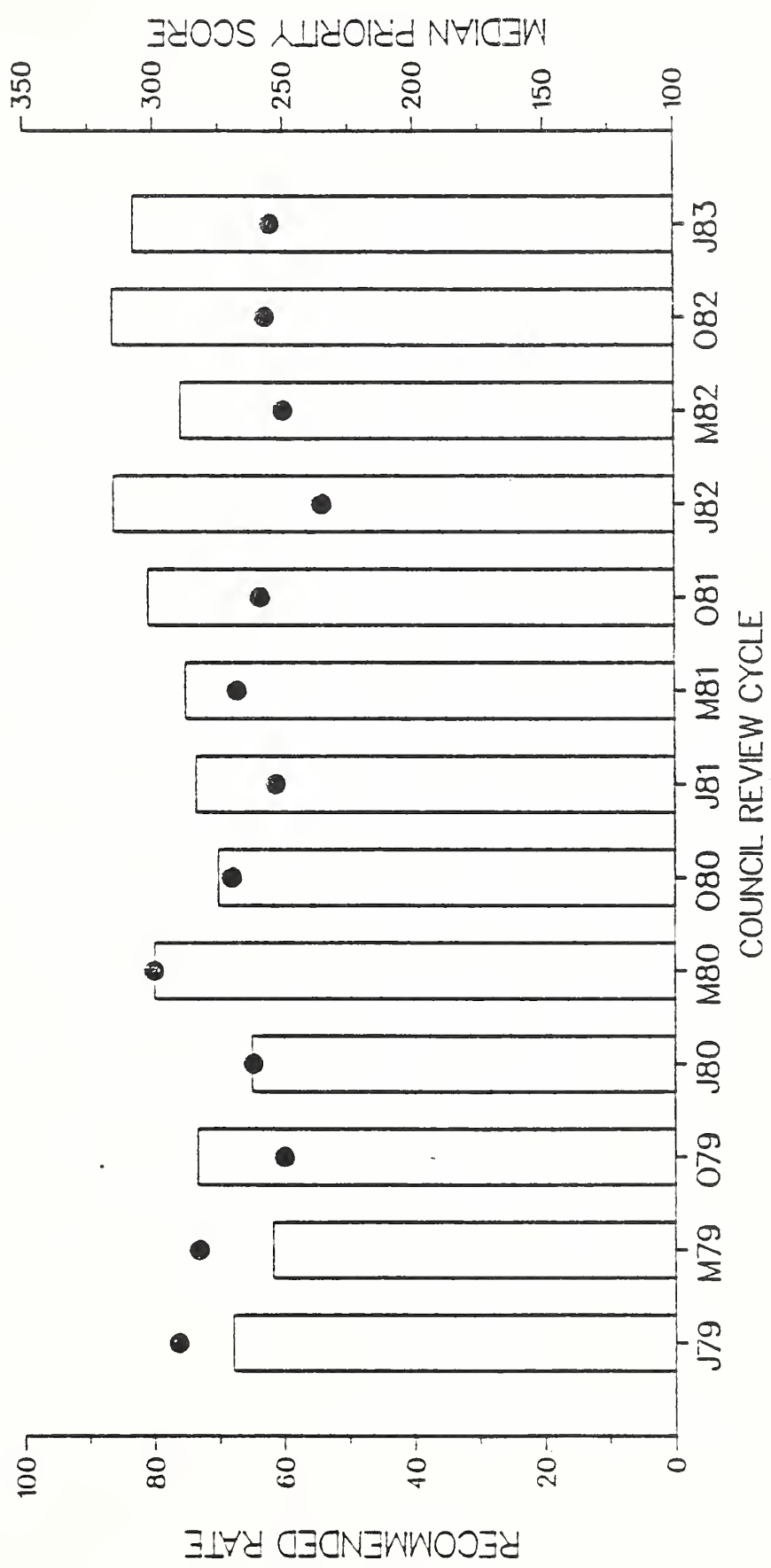


Rates are based on number of applications.  
Data are not shown if less than 10 applications were recommended for approval.  
Source: NII/DRG/SAB

# RECOMMENDED FOR APPROVAL RATES AND MEDIAN PRIORITY SCORE FOR RESEARCH PROJECTS JAN'79 - JAN'83

## STUDY SECTION: PTHB

(● = median priority score of approved applications)  
(bar = recommended rate)

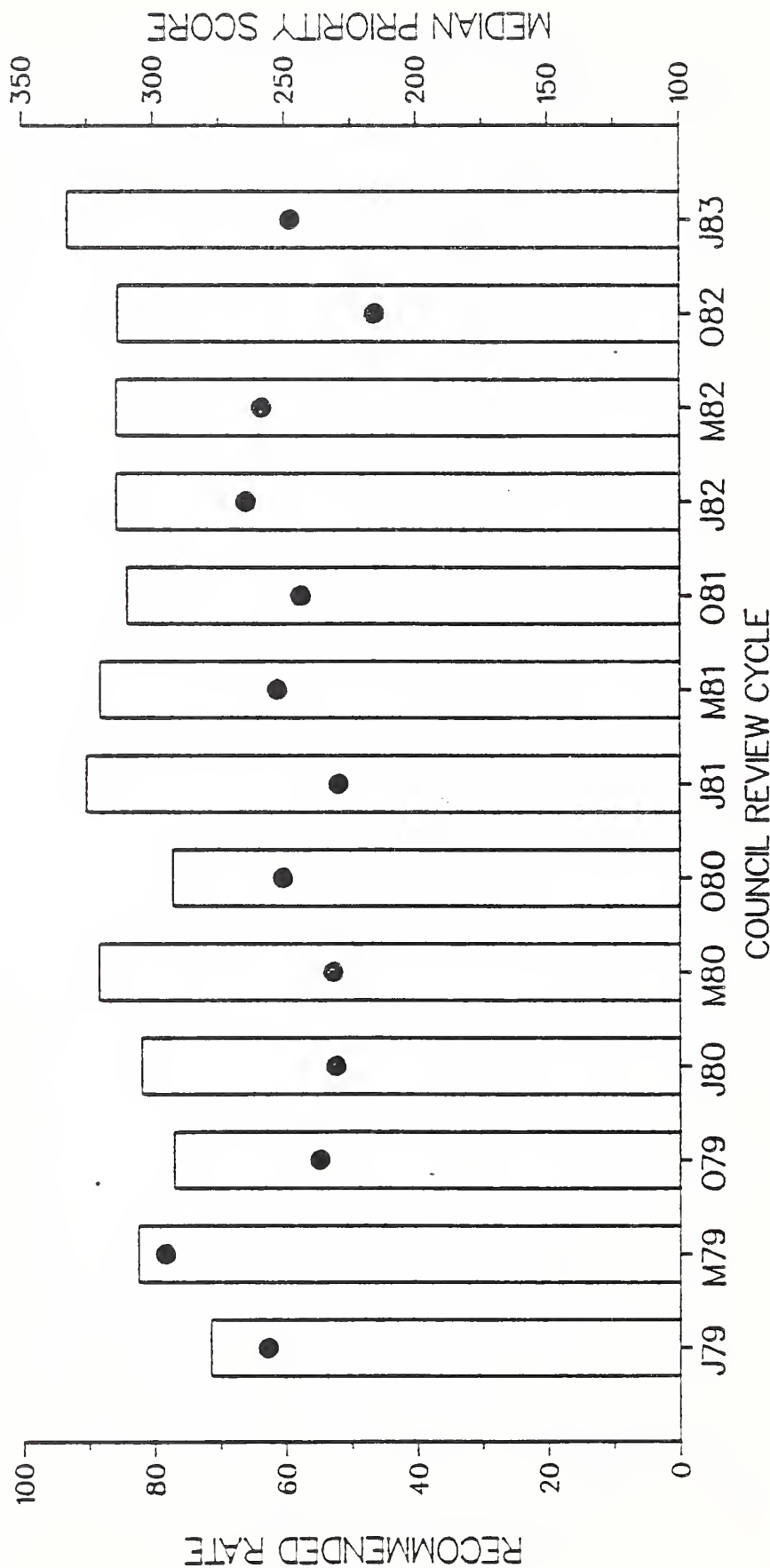


Rates are based on number of applications.  
Data are not shown if less than 10 applications were recommended for approval.  
Source: NIH/DRG/SAB

# RECOMMENDED FOR APPROVAL RATES AND MEDIAN PRIORITY SCORE FOR RESEARCH PROJECTS JAN'79 - JAN'83

## STUDY SECTION: RAD

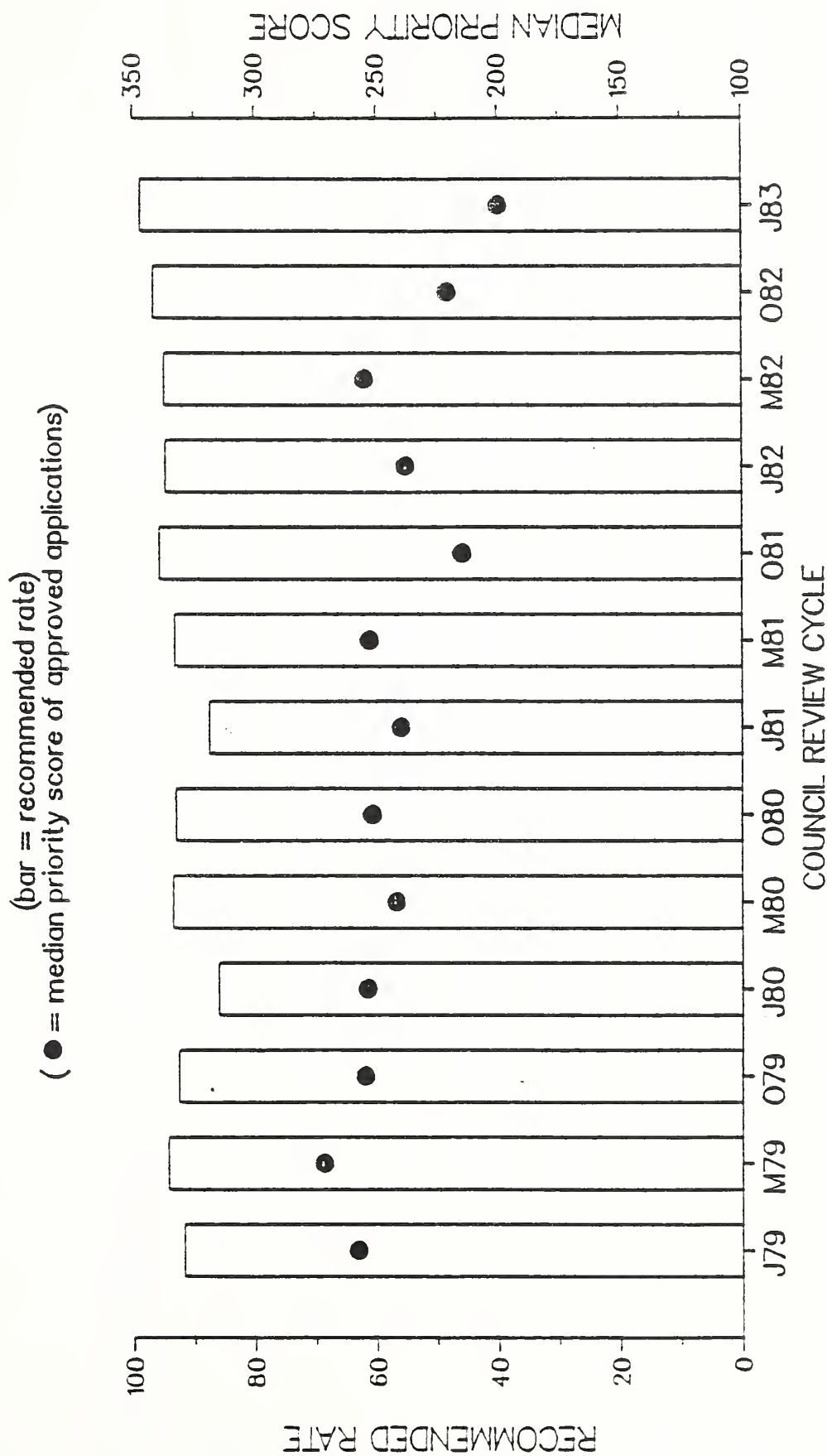
(● = median priority score of approved applications)  
(bar = recommended rate)



Rates are based on number of applications.  
Data are not shown if less than 10 applications were recommended for approval.  
Source: NIH/DRG/SAB

# RECOMMENDED FOR APPROVAL RATES AND MEDIAN PRIORITY SCORE FOR RESEARCH PROJECTS JAN'79 - JAN'83

## STUDY SECTION: VR



Rates are based on number of applications.  
Data are not shown if less than 10 applications were recommended for approval.  
Source: NII/DRG/SAB

REPORT 1.1.C

REPORT ON DRG STUDY SECTION ACTIONS FOR THE JAN 1983 COUNCIL MEETING (4)

RESEARCH GRANT APPLICATIONS TO BE REVIEWED, AND PRIORITY SCORES AT SPECIFIED PERCENTILES  
 APPLICATIONS REVIEWED FOR JAN 1983  
 \*\*\* APPLICATIONS REVIEWED FOR JAN 1983 AND PRECEDING TWO COUNCILS (1) \*\*\*

STUDY SECTION	REVD	APPR	REVMD	APPRV	PC	SCR	OVHL	10	20	25	26	27	28	29	30	31	32	33	34	40	50	60
ALY	8	8	85	77	91	229	79	141	152	159	160	162	163	166	167	169	170	171	171	182	206	237
BDCA	10	9	82	76	93	220	73	144	150	155	157	158	159	161	162	164	164	166	166	181	194	214
BDCE	1	0	74	68	92	227	89	138	148	150	151	153	154	155	156	157	160	161	163	171	200	225
BCE	26	24	86	81	94	228	58	150	164	172	173	174	176	177	179	182	184	184	185	200	215	232
BCE	16	11	77	69	64	282	95	140	161	178	183	188	192	194	193	208	221	226	236	259	292	308
BCE	12	11	97	89	92	222	76	144	157	169	171	171	173	178	180	181	182	185	189	199	221	239
BCE	15	11	62	53	85	248	78	154	169	181	183	185	188	189	193	197	201	203	207	227	250	264
BCE	1	1	64	55	86	239	78	144	153	163	164	165	167	171	174	176	179	181	182	193	221	242
BCE	1	1	70	68	97	245	82	151	170	186	189	191	194	198	201	202	202	204	207	218	234	249
BCE	6	6	55	46	84	220	67	146	167	172	174	176	177	178	178	181	181	182	183	199	227	254
BCE	27	24	59	55	93	232	67	156	171	181	182	183	184	189	192	193	193	194	195	202	222	237
BCE	0	0	77	62	81	256	93	137	152	161	165	169	173	176	178	181	182	184	186	208	250	279
CBY	8	6	62	56	90	238	83	136	149	156	157	160	163	165	168	169	171	173	177	190	222	246
CBY	0	0	53	44	83	222	83	140	148	157	160	161	161	163	165	166	167	169	170	188	224	266
CBY	20	20	68	64	94	227	69	153	171	179	181	181	184	185	188	193	195	196	198	209	232	246
CFA	97	76	105	84	80	265	95	149	168	173	174	176	177	177	180	181	182	184	185	209	251	281
CFA	13	11	79	70	89	235	74	140	151	159	160	161	161	164	164	166	168	170	172	191	222	249
CFA	1	0	44	38	89	287	87	163	187	194	197	204	207	208	211	214	218	219	222	230	264	293
CVB	0	0	49	44	90	240	75	153	164	168	169	169	169	170	173	176	178	179	180	194	232	251
ECS	0	0	53	41	77	240	63	157	176	186	188	189	191	192	193	193	194	194	197	210	234	266
EDC	10	6	61	32	52	234	75	144	164	171	171	171	172	173	174	175	175	176	177	187	208	240
EDC	26	22	53	37	70	259	83	155	169	186	186	186	187	188	189	190	193	193	194	216	242	278
ET	80	76	91	87	96	237	82	140	158	170	171	172	172	174	175	175	177	181	183	193	227	249
END	1	0	62	55	89	220	65	153	161	166	166	167	172	172	173	174	174	176	177	183	200	220
ET	119	103	122	106	87	241	66	166	176	181	183	187	183	189	191	194	195	197	203	227	254	274
EVR	35	33	79	73	92	233	82	146	162	167	168	172	174	177	179	180	184	185	186	211	235	253
GCH	3	2	56	52	93	231	89	141	149	152	153	154	154	159	159	163	163	165	167	186	217	256

\* INDICATES THAT THE PERCENTILE COMPUTATION INCLUDES A GENERATED VALUE WHICH IS LESS THAN THE LOWEST SCORE IN THE GROUP.  
 † BASED ON RECOMMENDATIONS BY DRG STUDY SECTIONS FOR ALL BIDS.  
 ‡ INCLUDES STUDY SECTIONS WITH 15 OR MORE RECOMMENDED APPLICATIONS (ALL BIDS) IN THE CURRENT ROUND AND AT LEAST 25 RECOMMENDED APPLICATIONS (ALL BIDS) IN THE LAST TWO ROUNDS. EXCLUDES SPECIAL STUDY SECTION (SSS).

## REPORT ON DRG STUDY SECTION ACTIONS FOR THE JAN 1983 COUNCIL MEETING (a)

RESEARCH GRANT APPLICATIONS TO BE REVIEWED, AND PRIORITY SCORES AT SPECIFIED PERCENTILES																									
*** APPLICATIONS REVITUL FOR JAN 1983 ***												PRIORITY SCORE AT EACH SPECIFIED PERCENTILE													
STUDY SECTION	<<HCI ONLY>>	<<< ALL BIDS >>>>	AVG	STD.	APPRV	REVMD	APPRV	PCT	SCR	DVHL	10	20	25	26	27	28	29	30	31	32	33	34	40	50	60
GEN	0	0	96	88	93	97	97	97	226	88	135	151	155	157	158	159	160	161	163	166	167	168	178	194	221
GIA	3	3	43	66	42	98	88	88	223	66	149	162	171	174	176	178	182	184	189	192	193	194	204	229	249
GNI	3	3	83	100	73	88	88	88	247	100	144	158	165	166	166	168	173	174	175	178	181	181	197	215	248
HOI 1	1	1	61	34	46	75	75	75	247	34	164	183	189	195	196	199	200	203	205	206	209	211	220	239	266
HOI 1	12	11	77	73	66	86	86	86	218	73	136	147	153	153	154	155	157	159	160	161	164	166	183	207	239
HOI 2	12	11	82	84	68	83	83	83	234	84	133	144	155	156	157	159	160	162	162	163	164	165	176	214	246
HOI 1	0	0	53	110	27	51	51	51	271	110	145	162	177	187	189	190	191	191	192	192	195	196	217	267	310
HOI 2	0	0	71	64	21	30	30	30	183	64	128	143	148	148	149	149	149	149	149	150	151	155	163	171	187
HOI 2	41	36	87	73	77	89	89	89	223	73	135	146	152	152	153	154	155	155	156	157	157	159	185	224	254
HOI 1	1	0	83	83	72	87	87	87	236	83	140	155	166	167	167	169	173	177	181	187	192	197	216	237	249
HOI 1	1	1	62	56	57	92	92	92	199	56	135	152	156	158	160	160	160	162	162	165	166	167	175	189	214
HOI 2	0	0	62	77	57	92	92	92	205	77	126	140	147	147	148	149	151	151	152	154	157	158	165	181	205
HOI 1	16	14	81	81	68	84	84	84	228	81	138	150	157	158	159	159	160	161	161	165	166	167	176	209	250
HOI 1	16	14	60	78	58	97	97	97	211	78	143	154	159	161	162	163	163	164	166	166	167	168	176	194	218
HOI 1	0	0	64	72	58	91	91	91	238	72	150	171	177	178	180	182	188	192	195	196	200	204	216	236	255
HOI 1	26	24	99	86	89	90	90	90	232	86	134	154	161	161	162	163	166	169	169	171	172	174	183	208	233
HOI 1	0	0	100	89	73	73	73	73	260	89	155	179	191	192	194	196	202	207	208	209	210	211	232	245	277
HOI 1	2	2	105	74	86	82	82	82	235	74	146	166	173	175	177	177	178	180	182	184	187	188	197	217	233
HOI 2	0	0	80	84	63	79	79	79	224	84	135	158	166	170	172	172	173	174	176	178	179	192	208	252	
HOI 2	0	0	94	74	77	82	82	82	217	74	137	155	165	167	169	170	171	173	175	177	179	180	190	212	228
HOI 2	10	4	60	83	45	75	75	75	240	83	143	167	185	187	189	190	192	196	200	202	203	204	231	252	285
HOI 1	1	0	56	84	38	68	68	68	236	84	144	175	183	183	184	186	189	193	196	196	199	219	249	270	
HOI 1	0	0	34	94	18	53	53	53	221	94	141	152	160	160	161	161	162	170	177	180	181	182	199	212	234
HOI 1	0	0	50	79	40	80	80	80	241	79	145	158	167	171	173	173	174	179	182	183	185	188	202	261	283
HOI 1	2	1	69	72	60	87	87	87	224	72	149	158	163	165	166	167	168	170	171	173	174	176	188	219	230
HOI 1	14	13	64	65	58	91	91	91	217	65	148	160	164	166	167	167	168	167	169	170	171	176	198	221	
HOI 1	8	7	88	67	84	95	95	95	219	67	148	163	167	168	168	169	169	171	172	173	175	176	186	205	224

\* INDICATES THAT THE PERCENTILE COMPUTATION INCLUDES A GENERATED VALUE WHICH IS LESS THAN THE LOWEST SCORE IN THE GROUP.

+ BASED ON RECOMMENDATIONS BY DRG STUDY SECTIONS FOR ALL BIDS.

\* INCLUDES STUDY SECTIONS WITH 15 OR MORE RECOMMENDED APPLICATIONS (ALL BIDS) IN THE CURRENT ROUND AND AT LEAST 25 RECOMMENDED APPLICATIONS (ALL BIDS) IN THE LAST TWO ROUNDS. EXCLUDES SPECIAL STUDY SECTION (S.S.S.).

REPORT ON DRG STUDY SECTION ACTIONS FOR THE JAN 1983 COUNCIL MEETING (R)

RESEARCH GRANT APPLICATIONS TO BE REVIEWED, AND PRIORITY SCORES AT SPECIFIED PERCENTILES

APPLICATIONS REVIEWED FOR JAN 1983

STUDY <HCL ONLY> <<< ALL BIDS >>> AVG STD. PRIORITY SCORE AT EACH SPECIFIED PERCENTILE

SECTION REVND APPR REVND APPR PCT SCR DVTH. 10 20 25 26 27 28 29 30 31 32 33 34 40 50 60

PHRA 1 0 62 55 250 78 155 183 191 193 156 197 198 199 201 202 202 204 219 241 266

PHY 0 0 73 63 225 88 135 153 158 160 161 161 161 162 163 165 166 167 178 209 240

PHIA 1 1 62 54 258 85 149 171 181 183 184 185 187 190 205 208 209 215 231 246 258

PHIB 88 72 103 83 244 68 151 166 174 181 183 185 190 191 196 199 201 203 226 254 275

RAD 64 59 72 66 251 78 159 168 174 174 177 179 179 181 184 186 188 191 205 237 270

RAP 1 1 87 68 259 90 157 172 176 178 181 182 183 187 188 192 194 198 218 251 273

RED 1 1 90 75 214 60 156 164 167 169 170 171 173 175 177 177 178 180 186 205 222

RUM 33 32 64 59 268 104 145 158 170 172 174 175 177 184 196 201 202 205 226 264 303

SAT 0 0 86 71 236 96 139 148 156 158 159 161 161 164 165 167 167 168 179 216 265

SD 5 4 71 57 241 70 148 165 174 176 178 179 182 184 187 190 194 197 212 225 258

SSP 0 0 52 41 298 119 137 154 161 164 169 170 173 185 195 200 216 227 267 314 348

TRP 0 0 70 64 222 80 130 144 148 149 152 153 155 157 159 160 161 161 177 201 222

TOX 12 11 86 71 256 87 159 194 205 206 210 212 215 217 219 222 226 228 243 262 284

VISA1 0 0 51 49 242 69 160 179 184 186 187 189 190 192 194 195 198 199 204 228 256

VISA2 0 0 70 62 236 83 146 167 172 172 173 174 176 177 179 181 181 183 191 210 243

VISA 0 0 62 51 220 69 148 158 162 163 166 166 169 169 170 171 172 173 185 201 227

VR 38 37 79 76 223 82 136 158 167 170 172 174 176 177 180 182 184 186 199 228 258

GRH TOT 949 824 5,129 4,342 235 82 145 160 167 169 171 172 174 176 178 180 182 184 198 224 250

\* INDICATES THAT THE PERCENTILE COMPUTATION INCLUDES A GENERATED VALUE WHICH IS LESS THAN THE LOWEST SCORE IN THE GROUP.  
+ BASED ON RECOMMENDATIONS BY DRG STUDY SECTIONS FOR ALL BIDS.  
# INCLUDES STUDY SECTIONS WITH 15 OR MORE RECOMMENDED APPLICATIONS (ALL BIDS) IN THE CURRENT ROUND AND AT LEAST 25 RECOMMENDED APPLICATIONS (ALL BIDS) IN THE LAST TWO ROUNDS. EXCLUDES SPECIAL STUDY SECTION (SSS).

## NEW LEAD DISCOVERY - THE GOAL OF THE DTP SCREENING EFFORT

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(new lead discovery component)	
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DTP, DCT, NCI

DCT ANTICANCER DRUG PROGRAM

- OBJECTIVE -

Discovery and development of new,  
clinically effective drugs

- GOAL -

New drugs for Phase I clinical trial  
(6 to 8 per year)

DTP NEW DRUG PROGRAM

<u>Components</u>	<u>Functions</u>
Drug Discovery	Acquisition and Screening Special Antitumor Testing
Pre-clinical Development	Large scale Production Formulation Toxicology

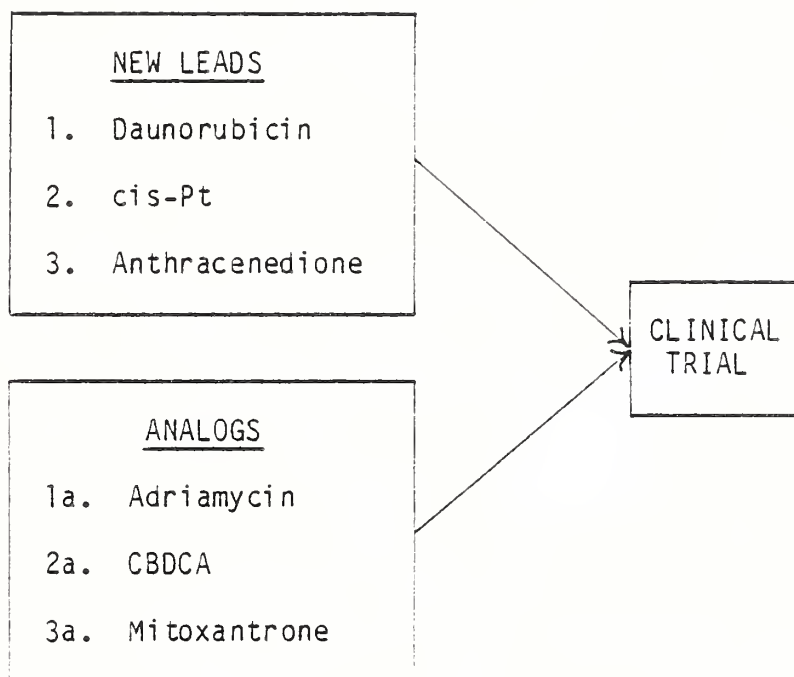
DRUG DISCOVERY COMPONENT

- OBJECTIVES -

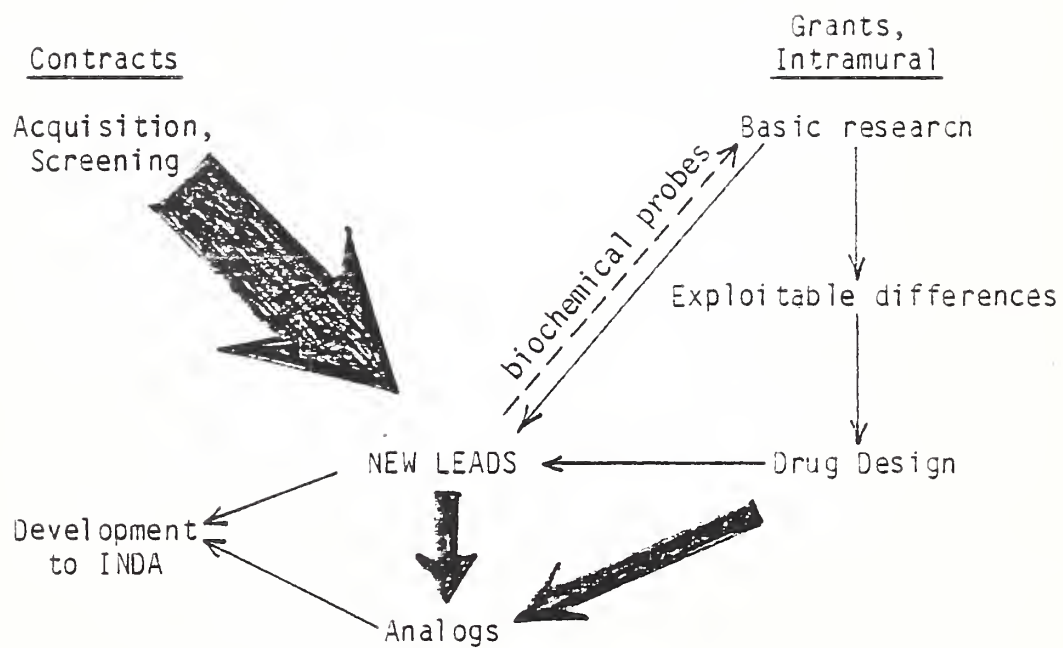
Major - New Lead Discovery

Other - Lead Improvement (Analogues)

NEW LEADS AND ANALOGS



NCI ANTICANCER DRUG DISCOVERY



Rational drug design accounts for the discovery of very few new leads in any area of medicinal chemistry. Screening and unexpected (serendipitous) observations are, and always have been, responsible for the vast majority of new lead discoveries. This is especially true in the area of chemotherapeutic drugs. Active natural products, such as adriamycin, are always empirically discovered. Rational drug design, however, is of major importance in the lead improvement (analog development) process.

The following paragraphs express opinions on this topic from people knowledgeable in non-cancer drug discovery fields. The NCI anticancer drug program is generally organized as described in 1), below. Our balanced program consists of long-term basic research (biochemistry and pharmacology grant program) coupled with selective screening (drug development contract program).

1) It is probably true to state that among the remarkable developments in antiparasitic drugs over the last 25 years, most have arisen from leads established by the selective or the intelligently applied empirical approaches. Few, if any, have arisen by the rational route, maybe because too little is known of the biochemistry of the relevant life-support systems or receptor sites.

In those parts of the pharmaceutical industry deploying significant R & D investment, the familiar pattern is a balanced programme of longterm basic research coupled with a "bread and butter" activity related to selective or empirical screening. Whatever the future success for the basic and rational approach, the erstwhile success of the other methods does not permit policy to forego the substance for the shadow.  
[O.D. Standen (1)]

2) Naturally, it would be desirable to find fundamental biochemical characteristics of diseases which can be modified through the antimetabolite, or other, approach. Unfortunately, in most diseases, medicinal agents are usually discovered by a screening technique or by accident. Therefore, the medicinal chemist's goal of designing new chemical agents, based on theoretical considerations, continues to prove elusive. [M. Gordon (2)]

3) During the past 20 years a large number of compounds have been introduced for the treatment of hypertension.

These agents have been developed as a result of an empiric approach to the medical management of essential hypertension. A completely rational search for effective chemotherapy is impossible because of our lack of understanding of the basic underlying mechanisms responsible for the elevation in systemic pressure. When it is possible to fully describe these factors, the course of therapeutic research will change abruptly. Until then, however, we are left with a research approach that remains empiric and dependent on the use of imperfect experimental models for the evaluation of potentially useful agents. [A.D. Bender (3)]

4) High-volume screening procedures are now being used in the search for new antimalarials, and are capable of handling as many as 600 new compounds per week; P. berghei in mice is the standard test infection, and P. gallinaceum in chicks is used to detect sporontocidal activity. [R.M. Pinder ("Antimalarials", p497, ref. 4)]

5) The screening tests for in vitro and in vivo antifungal action are quite similar to those employed for antibacterial potency. It is not difficult in the in vitro procedures to discover a reasonable number and variety of synthetic and natural compounds that are active in small quantities. But many of the substances detected by such screening must be eliminated from practical consideration after examination in systems in vivo. [E.D. Weinberg ("Antifungal Agents", p602, ref. 4)]

6) The ultimate test of anthelmintic activity is the ability of a chemical agent to eliminate worms from a specifically parasitized animal with a minimum of toxic effect to the host. Although at one time a suitable in vitro test was considered a useful screening method, current thinking is directed toward in vivo screening. In vivo screening methods enable the investigator to observe the potency of various drugs on the parasite in its natural environment, thereby presenting a truer picture of anthelmintic effect. [S. Tomcufcik and M. Hardy ("Anthelmintics", p584, ref. 4)]

7) Until more knowledge is available concerning the physiology and pathogenesis of E. histolytica, the search for new antiamebic drugs probably will consist mainly of empirically testing as many different substances as possible and of systematically examining chemical series that have already yielded useful drugs. [E.F. Elslager ("Antiamebic Agents", p523, ref. 4)]

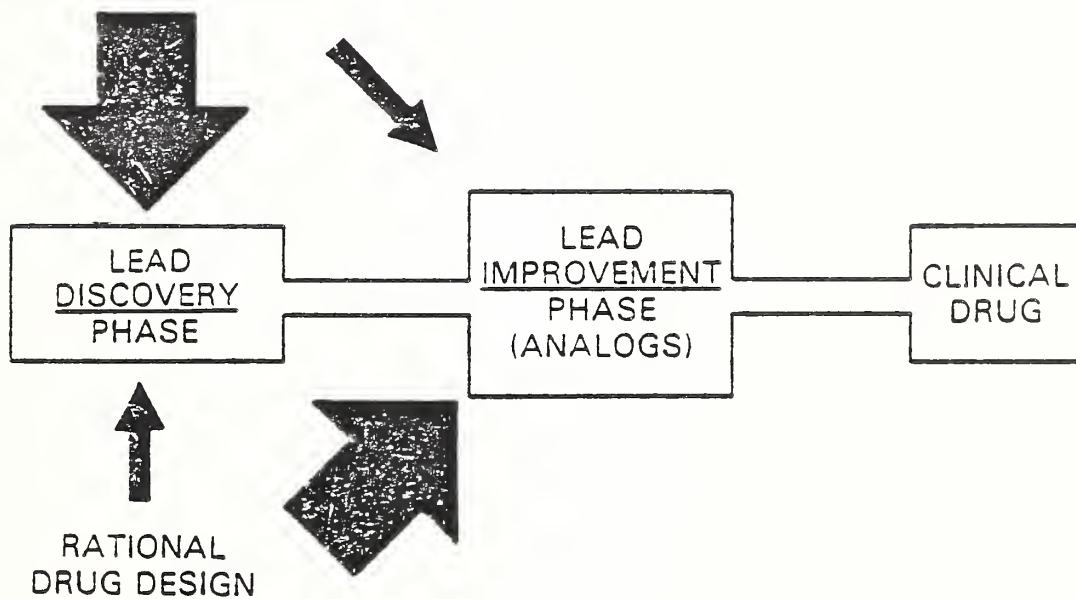
8) The purpose of screening is the discovery of new drugs which might be of use later in clinical medicine. Screening has the advantage over other more efficient procedures of uncovering unexpected chemical structural types as agents active under the test conditions. Such unanticipated compounds can then serve as starting points for further elaboration of suitable drugs. [A. Burger (5)]

#### References

1. O.D. Standen, "Pre-clinical Development of Drugs", in Development of Chemotherapeutic Agents for Parasitic Diseases, M. Marois, Ed., North-Holland, Amsterdam, 1975, p211.
2. M. Gordon, "Phenothiazine Drugs", in Topics in Medicinal Chemistry, Vol. 2, J. Rabinovitz and R. Myerson, Eds., Interscience, N.Y., 1968, p97.
3. A.D. Bender, "Antihypertensive Agents", in Topics in Medicinal Chemistry, Vol. 1, J. Rabinovitz and R. Myerson, Eds., Interscience, N.Y., 1967, p178.
4. Medicinal Chemistry, Part I, 3rd Ed., A. Burger, Ed., Wiley, N.Y., 1970.
5. A. Berger, "Approaches to Screening of Compounds for Pharmacological Activity", in Drug Development, C.E. Hamner, Ed., CRC Press, Boca Raton, 1982, p67.

## ROLE OF SCREENING VS. RATIONAL DRUG DESIGN

COMPOUND ACQUISITION  
AND SCREENING



SOME NON-ANTICANCER DRUGS  
DISCOVERED THROUGH SCREENING EFFORTS

Antimicrobials

Streptomycin  
Tetracycline  
Chloramphenicol  
Erythromycin  
Cephalosporins  
Amphotericin B  
Dapsone  
Isoniazid

Antimalarials

Antiamebics

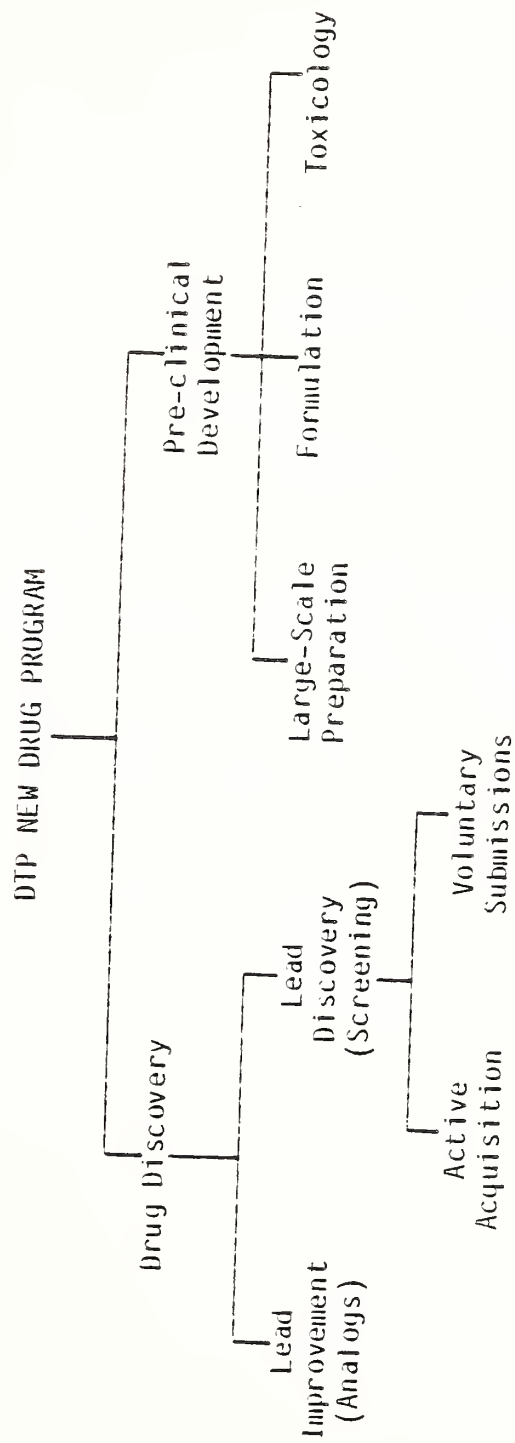
Anthelmintics

Sulfa drugs

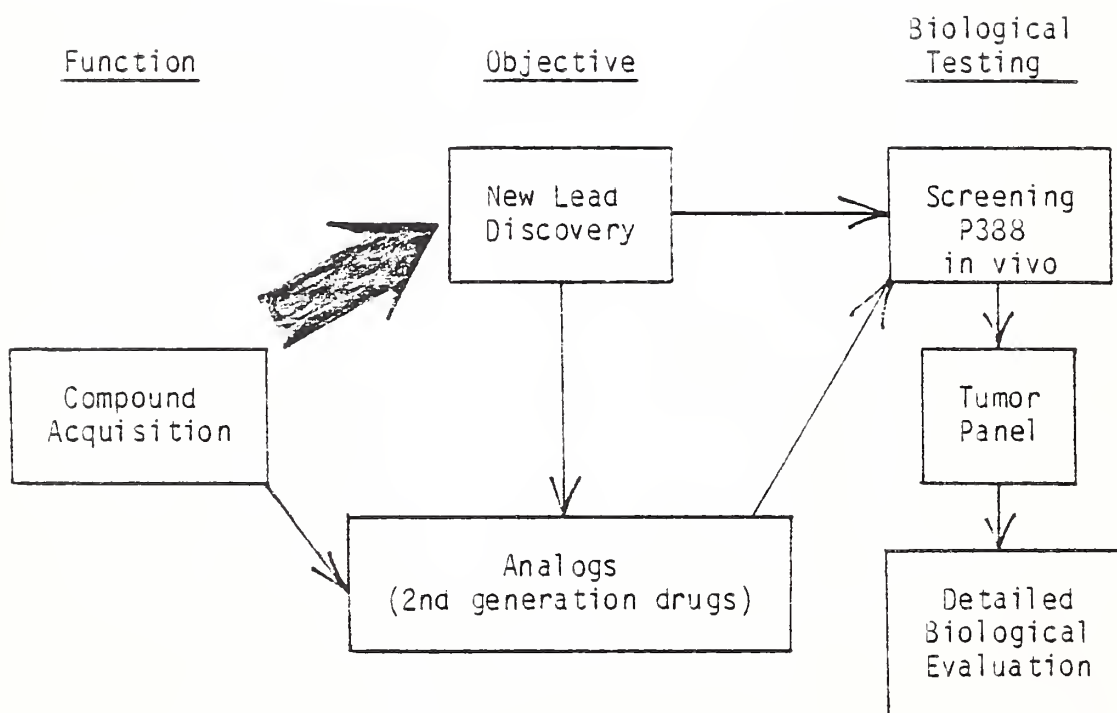
Valium

Dilantin

Thorazine



CONTRACT ACQUISITION AND TESTING



### ACQUISITION LIMITATIONS

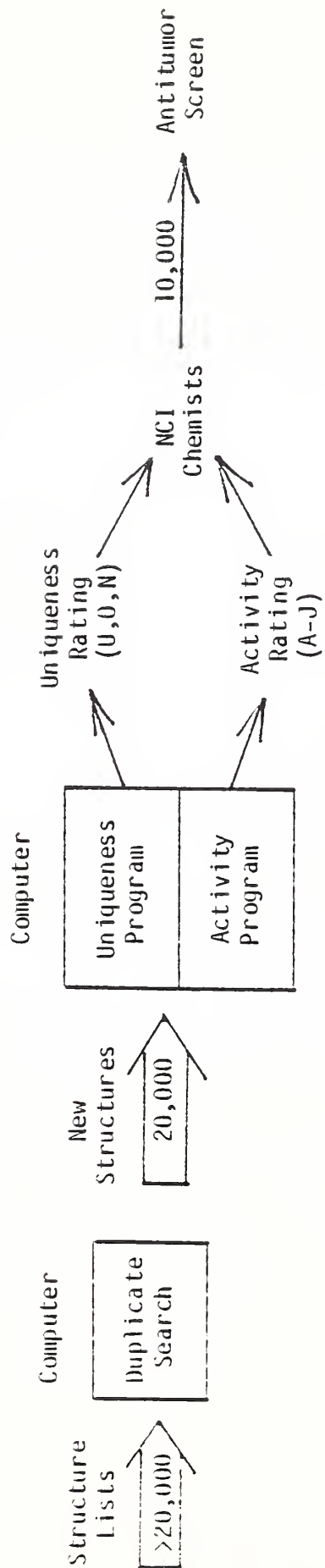
- A. Compound classes not generally accepted for screening when offered by suppliers

Nitrogen mustards  
Aziridines  
Nitrosoureas  
Triazenes (DTIC analogs)  
Epoxides

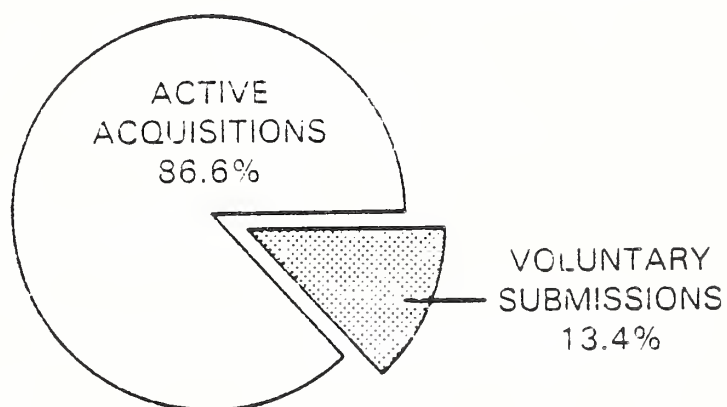
- B. Compound classes occasionally accepted for screening but not actively acquired

Anthracyclines  
Antifols  
Alkylating agents in general  
Platinums

ACQUISITION SELECTION PROCESS



## SOURCE OF COMPOUNDS 1977-1982



Active acquisitions are those compounds obtained as a result of a direct request by DCT staff or contractors.

TYPICAL TUMOR PANEL ACQUISITION DATA

SOURCE OF THE 231 TUMOR PANEL COMPOUNDS DERIVED FROM COMPOUNDS  
ACQUIRED DURING 1978

(NSC 295760-310831)

A. <u>Active Acquisitions (215)</u>	<u>Number</u>	<u>% of Grand Total</u>
1. Collection of synthetics		
a. Collection contractor	140	61
b. DCT staff (Europe)	23	10
c. Purchase, synthesis contractors	<u>22</u>	<u>9</u>
sub total	185	80
2. Collection of natural products DCT staff, contractors	<u>27</u>	<u>11.5</u>
total active acquisition	212	91.5
B. <u>Voluntary Submissions (16)</u>		
1. NCI grantees	6	3
2. DCT intramural program	2	1
3. Other	<u>11</u>	<u>4.5</u>
total voluntary submission	19	8.5
Grand total	231	100

PERFORMANCE OF STANDARD DRUGS IN THE NCI SCREEN

<u>Drug</u>	<u>Tumor Panel Systems with DN2 Level Activity*</u>
Cis-Platinum	B16,CD,L1210,LL,CX,MX
BCNU	B16,CD,L1210,LL,LX,MX
Melphalan	B16,CD,L1210,LX,CX,MX
Mitomycin C	B16,CD,L1210,LX,CX,MX
Cyclophosphamide	B16,CD,L1210,LL,MX
Adriamycin	B16,CD,L1210,LX,MX
Vincristine	B16,LX,MX
Ara-C	L1210,LL,MX
6-MP	L1210
Methotrexate	L1210
Bleomycin	None

B16	- B16 melanoma
CD	- CD8F <sub>1</sub> mouse mammary
L1210	- L1210 leukemia
LL	- Lewis lung mouse
CX	- Colon xenograft
LX	- Lung xenograft
MX	- Mammary xenograft

\*All drugs also possess at least minimum P388 pre-screen activity.

## NEW DRUG PROGRAM STATISTICS

- A. Pre-Screen (P388 Leukemia)
  - ° 10,000 new compounds tested per year
  - ° Ca. 5% (500) active (ILS > 20%)
- B. Screen (Current Tumor Panel: L1210; B16; M5076; Mammary Xenograft)
  - ° 250 compounds tested per year
  - ° Ca. 20 actives (Decision Network criteria)
- C. Decision Network Authorized Further Evaluation
  - ° 8-10 compounds per year selected as potential clinical candidates (large-scale production, formulation development, special biological evaluation)
  - ° 7-9 compounds per year put through the NCI toxicology protocol
- D. DCT Investigational New Drug Applications (INDA)
  - ° 6-8 per year

COMPOUNDS CURRENTLY IN PRE-CLINICAL DEVELOPMENT  
(DCT Decision Network Status 2A or 2B, January 1, 1983)

<u>NSC</u>	<u>Compound*†</u>	<u>Antitumor Discovery Institution**</u>	<u>NCI Pre-Clinical Role</u>
127755	Dihydrotriazine (B.R. Baker)	NCI (Voluntary)	discovery
156492D	Discreet	NCI (Acquisition)	discovery
226080	Rapamycin (Ayerst)	NCI (Acquisition)	discovery
234714	Aphidicolin (ICI)	NCI (Acquisition)	discovery
237020	Largomycin (Tanabe Inc.)	Tanabe (Acquisition)	significant
253272	Caracemide (Dow)	NCI (Acquisition)	discovery
261726	3-Deazaguanine (ICN)	ICN, U.S.C. (Voluntary)	little
267213	Sulfonyl hydrazone	NCI (Stanford R.I.)	discovery
268242	N-Dibenzyl daunorubicin	NCI (Stanford R.I.)	discovery
269148	Menogarol	NCI (Upjohn)	discovery
271674	DACH	NCI (Gale)	discovery
278214	Isopropyl Pyrrolizine (SUNY)	NCI (Voluntary)	discovery
281272	Ara AC	NCI (Intramural)	discovery
283162	Trimethyl TMM	C. Beatty (Voluntary)	significant
284356	Bisimide (Gulf)	NCI (Acquisition)	discovery
293015	Lipha Compound (Lipha)	NCI (Acquisition)	discovery
303861D	Discreet	NCI (Acquisition)	discovery
308847	Benzoisoquinolinedione (Spain)	NCI (Acquisition)	discovery
314055	Radiosensitizer SR 2555	NCI (Stanford R.I.)	discovery
322921	Bisbenzimidazole (Purchase)	NCI (Acquisition)	discovery
325014	Bactobolin (IMC)	IMC (Acquisition)	significant
325319	Didemnin B	NCI (U. Oklahoma)	discovery
328426	Phyllanthoside	NCI (U. Virginia)	discovery
330500	Macbecin II (Takeda Inc.)	Takeda (Acquisition)	significant
333856D	Discreet	Non-NCI (Acquisition)	significant
339638D	Discreet	NCI (Contract)	discovery
352122	Trimetrexate (Warner-Lambert)	NCI (Voluntary)	discovery

\*Name in parenthesis indicates acquisition source

†See Abbreviations section

\*\*Word in parenthesis indicates submission mode (voluntary submission, active acquisition, intramural program or NCI contractor responsible for the compound). NCI funded discovery (excluding grants) is shown here and in subsequent tables with NCI as discovery institution.

ANALYSIS OF THE 27 COMPOUNDS CURRENTLY IN PRE-CLINICAL DEVELOPMENT  
(SEE PREVIOUS PAGE)

Source Analysis

<u>A. Active Acquisition (21)</u>	<u>Number</u>	<u>% of Grand Total</u>
1. Synthetics		
a. Collection contractor	4	15
b. DCT staff (Europe)	2	7
c. Purchase, synthesis contractors	<u>5</u>	<u>18.5</u>
sub total	11	40.5
2. Natural Products		
a. DCT staff	6	22.5
b. Fermentation contractors	2	7
c. Plant and animal contractors	<u>2</u>	<u>7</u>
sub total	10	36.5
total active acquisition	21	77
 B. <u>Voluntary Submissions (6)</u>		
1. NCI grantees	1	4
2. DCT intramural program	1	4
3. Other	<u>4</u>	<u>15</u>
total voluntary submission	6	23
Grand total	27	100

Discovery of Antitumor Activity

	<u>Number</u>	<u>%</u>
NCI	21	78
Other	<u>6</u>	<u>22</u>
Total	27	100

<u>Year</u>	<u>NSC</u>	<u>Compound**</u>	<u>Antitumor Discovery Institution**</u>	<u>NCI Pre-Clinical Role</u>
1977	51143	IMPY (Ciba)	Ciba (Voluntary)	significant
	132319	Indicine-N-oxide	NCI (Pfizer)	discovery
	165563	Bruceantin	NCI (U. Virginia)	discovery
	177023	Levamisol (Lederle)	Janssen (Acquisition)	little
	224131	PALA (Stark, Stanford U.)	NCI (Acquisition)	discovery
	249992	Amsacrine (Cain, N.Z.)	New Zealand (Voluntary)	significant
	261037	Oral Misonidazole	Roche (Voluntary)	little
1978	15780	Amygdalin	Not applicable	-
	21548	Thymidine	NCI (Stehlin)	discovery
	95466	PCNU	NCI (So.R.I.)	discovery
	118742	PMM	NCI (C. Beatty)	significant
	134454	THC	Not applicable	-
	153353	Alanosine (LePetit)	MSKCC (Acquisition)	significant
	169870	ICRF-187 (ICRF)	ICRF (Acquisition)	significant
	302357	Heroin	Not applicable	-
1979	7365	DON (So.R.I.)	NCI† (Voluntary)	discovery
	163501	AT-125	NCI (Upjohn)	discovery
	182986	AZQ	NCI (Intramural)	discovery
	208734	Aclacinomycin (IMC)	IMC (Acquisition)	little
	218321	Deoxycoformycin (Parke-Davis)	NCI (So.R.I.)	discovery
	261037	I.V. Misonidazole	Roche (Voluntary)	none
	301739	Mitoxantrone (Allied, MRI)	NCI (Acquisition)	discovery
1980	139490	Ketotrexate	NCI (Intramural)	discovery
	261036	Desmethylnisonidazole	Roche (Voluntary)	none
	296961	WR-2721	Walter Reed	little
	331615	Levonantradol	Not applicable	-
	404241	AraA	NCI (So.R.I., MDA)	discovery
1981	40774	6-MMPR	NCI (MSKCC, So.R.I.)	discovery
	141633	Homoharringtonine (USDA)	NCI (Acquisition)	discovery
	192965	Spirogermanium	Georgetown U. (Voluntary)	little
	241240	C8DCA	NCI (C. Beatty)	significant
	264880	Dihydro-5-azacytidine	NCI (Intramural)	discovery
	280594	Tricyclic nucleotide	NCI (Utah)	discovery
	296934	Teroxirone (Henkel)	NCI (Acquisition)	discovery
	337766	Bisanthrene	Lederle (Voluntary)	none
	526417	Echinomycin (Shionogi Inc.)	MSKCC (Acquisition)	significant
1982	3051	N-Methylformamide (So.R.I.)	NCI† (Voluntary)	discovery
	172112	Spiromustine	NCI (Intramural)	discovery
	286193	Tiazofuran (ICN)	NCI (Acquisition)	discovery
	301467	Radiosensitizer SR2508	NCI (Stanford R.I.)	discovery
	305884	Acodazole (Norwich)	NCI (Acquisition)	discovery
	312887	Fludarabine	NCI (So.R.I.)	discovery

\*Name in parenthesis indicates acquisition source

†See Abbreviations section

\*\*Word in parenthesis indicates submission mode (voluntary submission, active acquisition, intramural program or NCI contractor responsible for the compound)

†INDA based on new NCI tumor panel models

ANALYSIS OF THE 33 NCI INDIA FOR CYTOXIC AGENTS (1977-1982)  
(SEE PREVIOUS PAGE)

Source Analysis

A. <u>Active Acquisition (23)</u>	<u>Number</u>	<u>% of Grand Total</u>
1. Synthetics		
a. Collection contractor	5	15
b. DCT staff (Europe)	2	6
c. Purchase, synthesis contractors, other	9	27
	<hr/>	<hr/>
sub total	16	48
2. Natural Products		
a. DCT staff	4	12
b. Fermentation contractors	1	3
c. Plant and animal contractors	2	6
	<hr/>	<hr/>
sub total	7	21
total active acquisition	23	69
 B. <u>Voluntary Submissions (10)</u>		
1. NCI grantees	0	0
2. DCT intramural program	4	12
3. Other	6	18
	<hr/>	<hr/>
total voluntary submission	10	30
Grand total	33	99

Discovery of Antitumor Activity

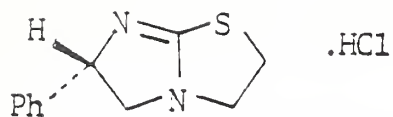
	<u>Number</u>	<u>%</u>
NCI	24	73
Other	<hr/> 9	<hr/> 27
Total	33	100

# SOURCES OF NEW LEADS

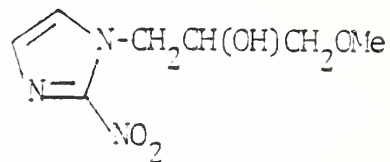
33 NCI INDIA FILED FOR CYTOTOXIC AGENTS (1977-1982)

<u>Source</u>	<u>New Leads</u>	<u>Analogs</u>
A. Synthetic Compounds		
1. Collection contractor	5	0
2. DCT staff (Europe)	0	2
3. Purchase, other	1	1
4. Synthesis contractors	1	6
5. Voluntary submissions	6	4
B. Natural Products		
1. Natural Products Branch staff	3	1
2. Natural Products contractors	<u>3</u>	<u>0</u>
	19	14

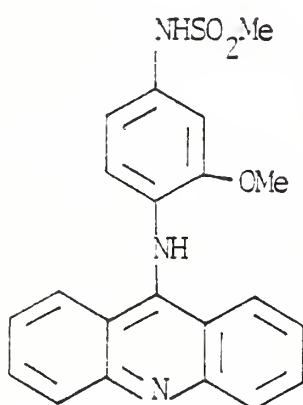
INVESTIGATIONAL NEW DRUG APPLICATIONS-1977



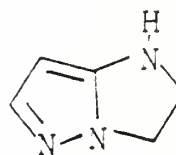
Levamisole  
NSC 177023



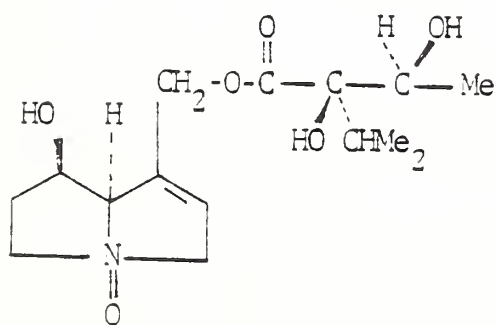
Misonidazole-PO  
NSC 261037



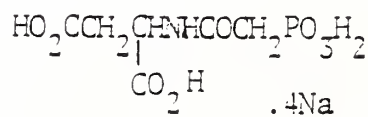
m-AMSA  
NSC 249992



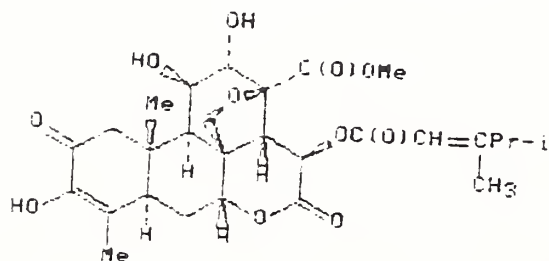
Pyrazolo-Imidazole  
NSC 51143



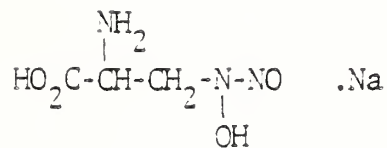
Indicine-N-Oxide  
NSC 132319



PALA  
NSC 224131

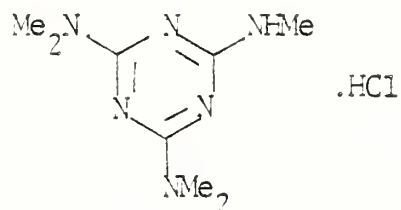


Bruceantin  
NSC 165363



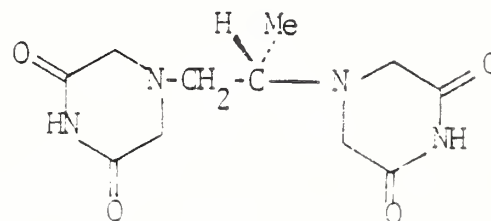
L-Alanosine

NSC 153353



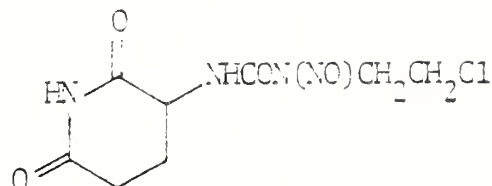
Pentamethylmelamine

NSC 118742



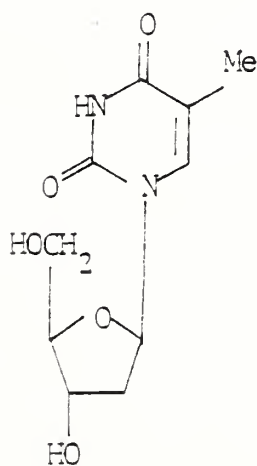
ICRF-187

NSC 169780



PCNU

NSC 95466



Thymidine

NSC 21548

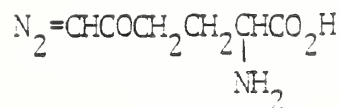
THC

NSC 154454

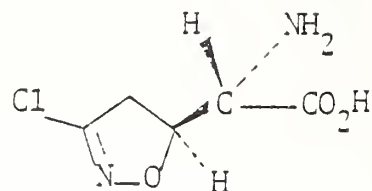
Heroin

NSC 302357

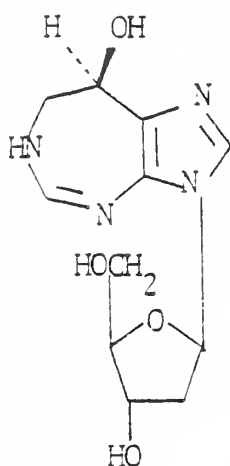
INVESTIGATIONAL NEW DRUG APPLICATIONS-1979



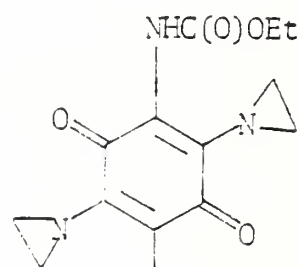
DON  
NSC 7365



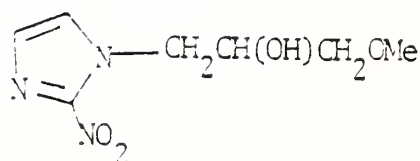
AT-125  
NSC 163501



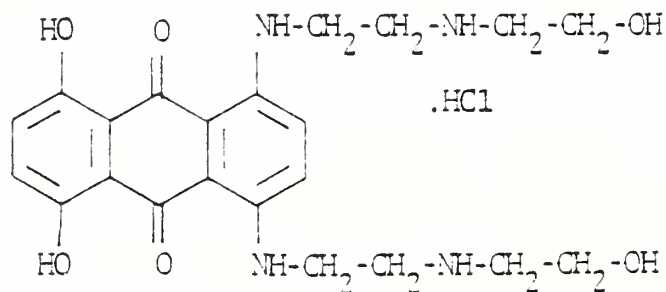
2'-Deoxycoformycin  
NSC 218321



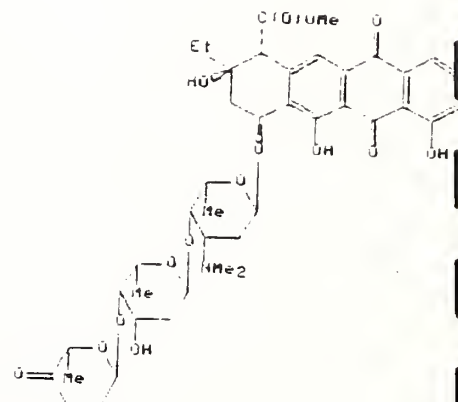
AZQ  
NSC 182986



Misonidazole-IV  
NSC 261037

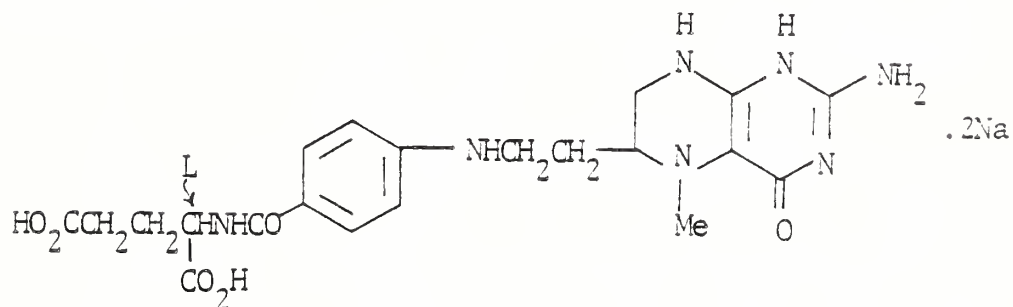


Mitoxantrone  
NSC 301739



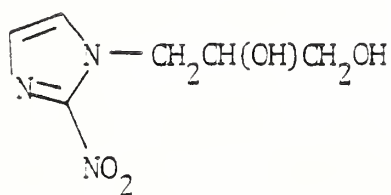
Aclacinomycin  
NSC 108734

INVESTIGATIONAL NEW DRUG APPLICATIONS-1980



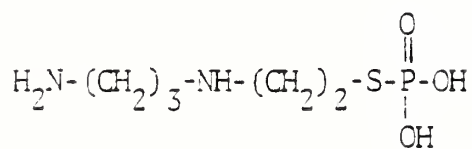
5-Methyltetrahydrohomofolate

NSC 139490



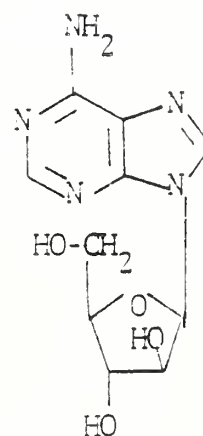
Desmethylnisonidazole

NSC 261036



WR-2721

NSC 296961

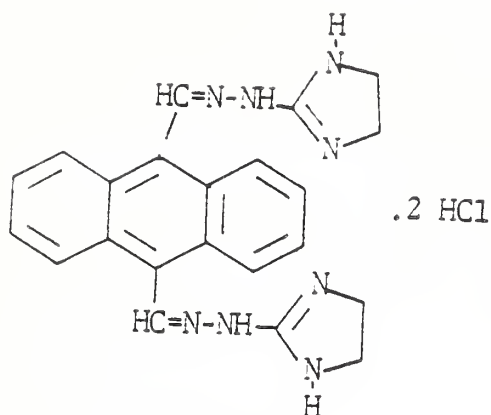


ARA A

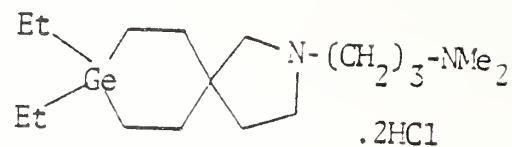
NSC 404241

Levonantradol

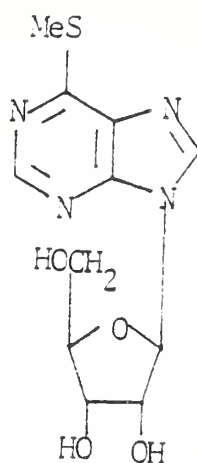
NSC 331615



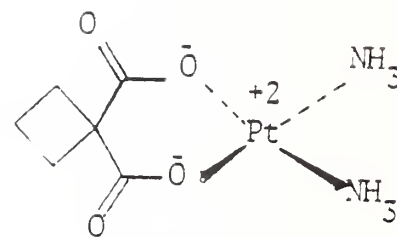
Bisantrene  
NSC 337766



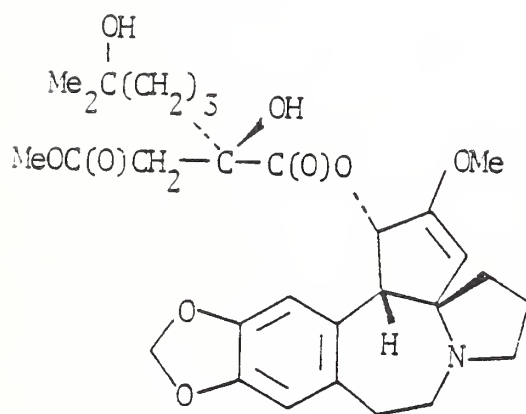
Spirogermanium  
NSC 192965



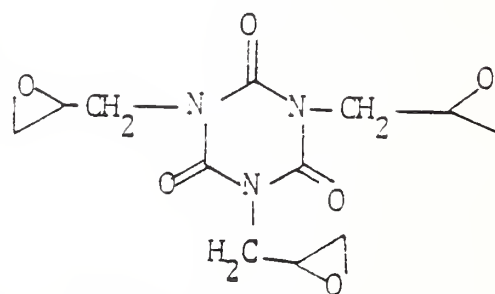
6-Methylmercapto-  
Purine Riboside  
NSC 40774



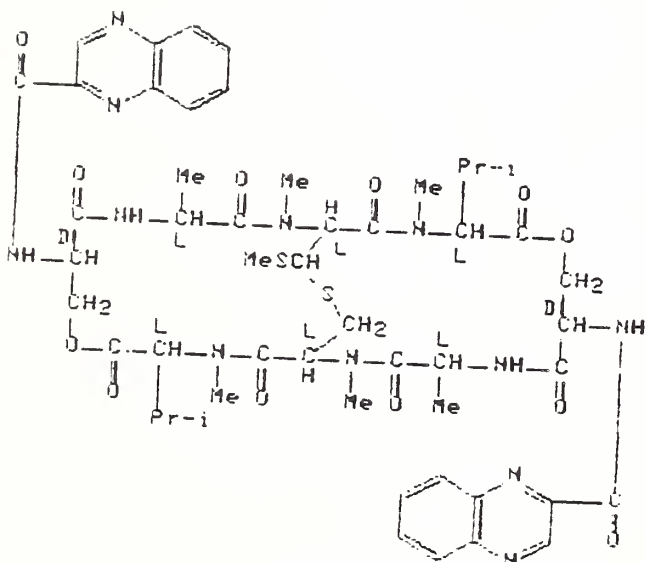
CBDCA  
NSC 241240



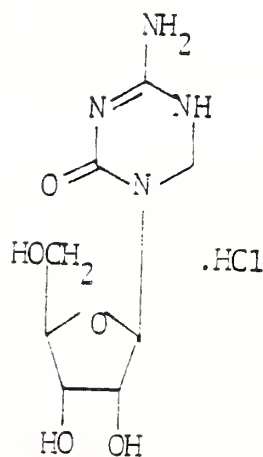
Homoharringtonine  
NSC 141633



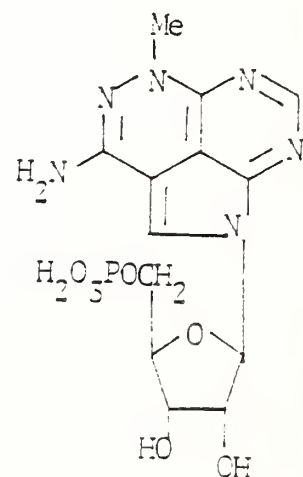
Henkel's Compound  
NSC 296934



Echinomycin  
NSC 526417

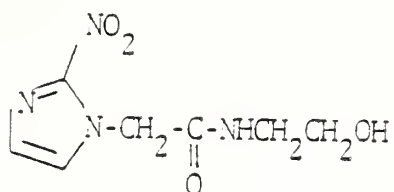


5,6-Dihydro-5-  
Azacytidine  
NSC 264880

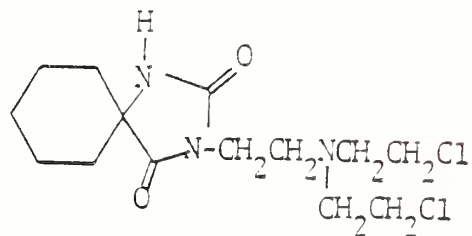


Tricyclic Nucleoside  
3'-Phosphate  
NSC 280594

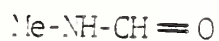
-27-  
INVESTIGATIONAL NEW DRUG APPLICATIONS-1982



SR 2508  
NSC 301467

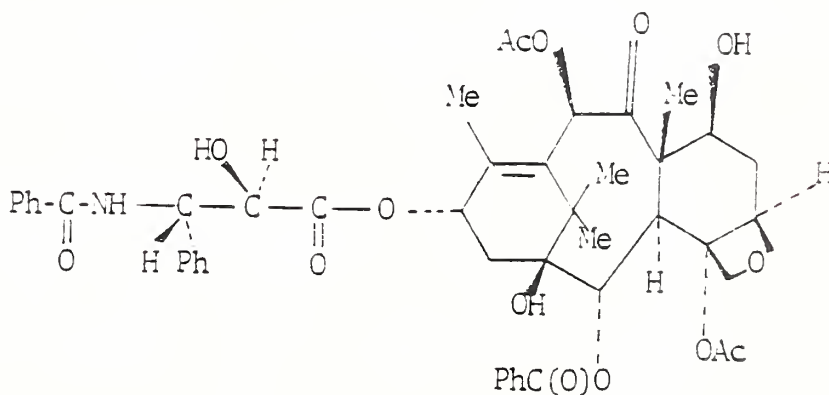


Spiromustine  
NSC 172112

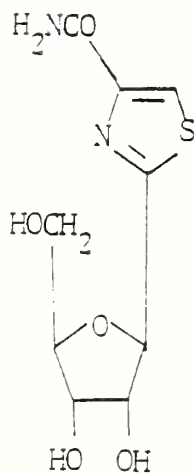


N-Methylformamide

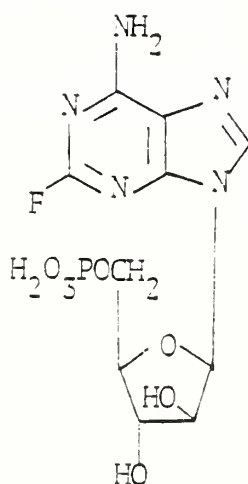
NSC 3051



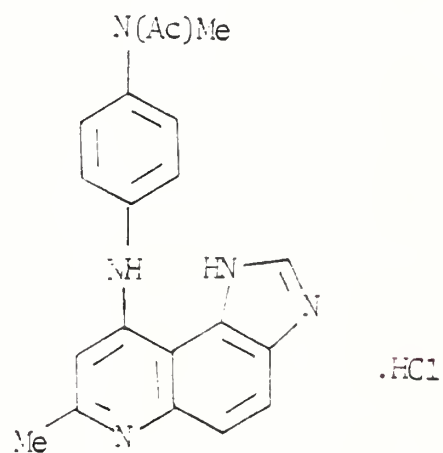
Taxol (February 1983)  
NSC 125973



Tiazofurin  
NSC 286193



Fludarabine Phosphate  
NSC 312887



Acodazole HCl  
NSC 305384

Examples of Synthetic Anticancer Drugs Based on  
Leads Discovered in the NCI Screening Program \*

Nitrosoureas

409962

BCNU



079037

CCNU



095441

MeCCNU

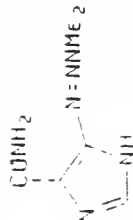


095466

PCNU

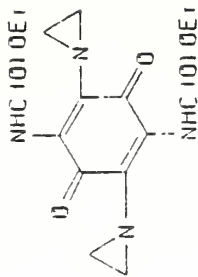


NSC 45300



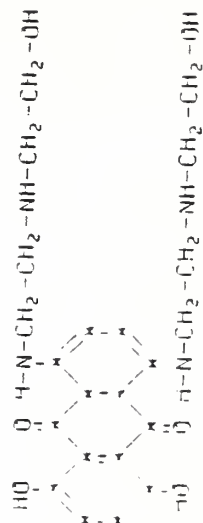
DTIC

NSC 102986



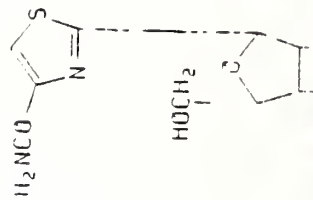
AZQ

NSC 301739



Mitoxanthrone

NSC 286193



Tiazofurin

TYPICAL TIME FRAME FOR DCT NEW DRUG OPERATIONS

<u>Operation</u>	<u>Approximate Time to Completion (Cumulative)</u>
1. Pre-screen activity discovered and confirmed	6 months
2. Tumor panel activity confirmed	2 years
3. Pass DN2A (start formulation development, large scale production)	3 years
4. Pass DN2B (start toxicology)	5 years
5. INDa filed	6 years
6. Phase I clinical studies completed (Safety)	7 years
7. Phase II clinical studies completed (Effectiveness)	9 years
8. Phase III clinical studies completed (Comparison)	12 years
9. NDA approved	14 years

ORIGIN OF 32 COMMERCIALY AVAILABLE ANTICANCER DRUGS

A. Drugs with Publication Dates which Indicate Discovery was Made Prior to Start of the NCI New Drug Program in 1955

<u>Drug</u>	<u>Antitumor Discovery (Institution)*</u>	<u>Antitumor Publication</u>	<u>NDA</u>
1. Nitrogen mustard	U.S. Army (Yale)	1946	1949
2. Methotrexate	MSKCC, Lederle	1949	1953
3. Triethylenemelamine	Lederle	1950	1953
4. Busulfan	Chester Beatty	1951	1954
5. Thiotepa	Lederle	1952	1959
6. 6-Mercaptopurine	Wellcome, MSKCC	1953	1953
7. Chlorambucil	Chester Beatty	1953	1957
8. Thioguanine	Wellcome, MSKCC	1954	1966
9. Melphalan	Chester Beatty	1954	1964
10. Actinomycin D	Children's Med. Center	1955	1964
11. Mitomycin C	Inst. Microb. Chem.	1956	1974
12. 5-Fluorouracil	U. Wisconsin	1957	1962
13. FUOR	U. Wisconsin	1957	1970
14. Vinblastine	Lilly	1958	1961
15. Cyclophosphamide	Asta Werke	1958	1959
16. Uracil mustard	Upjohn	1958	1962

\*See Abbreviations section

COMMERCIALLY AVAILABLE DRUGS (CONTINUED)

8. Drugs with Publication Dates after 1958

<u>Drug</u>	<u>Antitumor Discovery (Institution)*</u>	<u>Antitumor Publication</u>	<u>NDA</u>	<u>NCI Pre-Clinical Role**</u>
1. o,p-DDD	NCI (Intramural)	1959	1970	discovery
2. Mithramycin	NCI (Pfizer)	1960	1970	discovery
3. Ara-C	Upjohn	1961	1969	significant
4. DTIC	NCI (So.R.I.)	1962	1975	discovery
5. Vincristine	Lilly	1962	1963	none
6. Pipobroman	NCI (Abbott)	1962	1966	discovery
7. Streptozotocin	NCI (Upjohn)	1962	1982	discovery
8. Hydroxyurea	NCI (Squibb)	1963	1967	discovery
9. Procarbazine	Roche	1963	1969	none
10. BCNU	NCI (So.R.I.)	1963	1977	discovery
11. L-Asparaginase	Cornell	1963	1978	significant
12. Daunorubicin	Farmitalia, Rhone Poulenc	1963	1979	little
13. Bleomycin	IMC	1965	1973	little
14. CCNU	NCI (So.R.I.)	1966	1976	discovery
15. Adriamycin	Farmitalia	1968	1974	little
16. Cisplatin	Michigan State	1969	1978	significant

\*See Abbreviations section

\*\*NCI had a major role in the clinical development of all these drugs

GROUP C DRUGS

<u>NSC</u>	<u>Drug</u>	<u>Indication</u>	<u>Antitumor Discovery (Institution)</u>	<u>Antitumor Publication</u>
13875	Hexamethylmelamine	CA-ovary	MSKCC	1950
95441	MeCCNU	CA-colon and stomach Melanoma	NCI (So.R.I.)	1963
102816	5-Azacytidine	Refractory AML	Czech (Sorm)	1964
106977	Asparaginase (Erwinia)	ALL	Microbial Research Establishment	
134454	THC	Anti-emetic	Not applicable	-
141540	VP-16 (Etoposide)	CA-lung (small cell)	Sandoz	1963
249992	Amsacrine	Refractory AML	New Zealand Cancer Soc. (Cain)	1974

SUMMARY

1. The DTP compound acquisition and screening effort is an important component of the NCI anticancer drug development program which spans discovery (acquisition, screening) and pre-clinical development (large scale production, dose formulation, pharmacology and toxicology). The major purpose of the acquisition and screening component is new lead discovery.
2. With anticancer drugs, as with drugs in all areas of medicinal chemistry, new leads are discovered most often through screening (eg. anthracenedione) or serendipity (eg. cis-platinum). Leads, once discovered, are efficiently optimized through rational drug design procedures.
3. Natural product leads (eg. daunorubicin/adriamycin, vincristine) are always the result of empirical discovery.
4. DCT funded efforts (contract and intramural, but excluding grants) discovered the antitumor activity of 24 (73%) of the 33 cytotoxic agents which DCT entered into clinical trial during the period 1977-1982. Of these compounds, 11 were derived from synthesis or natural product contractors, 7 from active acquisition, 4 from the DCT intramural program and 2 from the re-screening of older compounds in new tumor models. The DTP played an important role in the pre-clinical development of over 90% of these agents.
5. Mitoxanthrone (INDA 1979) is an example of a clinically promising drug acquired by the DTP selective acquisition process. Tiazofurin (INDA 1982), acquired in the same manner, has exciting potential based on its unusual activity against lung tumor models. AZQ (INDA 1979) was rationally designed to cross the blood-brain-barrier and have activity against brain tumors. This type activity has been observed clinically. AZQ's rational design, however, is based on a lead compound originally discovered in the NCI screen. The four nitrosoureas introduced into clinical trial all owe their existence directly to a nitroguanidine discovered to be active in the DTP screening program. DTIC also originated from the DTP screening process. Amsacrine was discovered in a New Zealand screening program.

6. The DCT drug discovery effort is, and always has been, a designed experiment. This experiment attempts to discover new drugs at the same time it tests activity correlations between animal tumor models and clinical cancers. Because our tumor models are still imperfect, screening for new lead discovery is not a very efficient process (10 out of 10,000 compounds tested are chosen as clinical candidates). For the same reason, one should expect that not all drugs introduced into clinical trial will have significant antitumor activity.
7. There are many useful anticancer drugs available today. Few people would suggest, however, that the existing drugs are good enough. Many years of experience also suggest that new analogs of the existing drugs will not satisfy our need for superior agents. New agent classes with different or improved mechanisms of action are required. The DCT Biochemistry and Pharmacology Grant Program seeks fundamental information which may be useful in the rational discovery of new antitumor agents. The National Cooperative Drug Discovery Group initiative is DCT's most recent attempt to accelerate the transfer of basic science into rational lead discovery and new clinical agents. However, until the basic science of cancer yields information which allows the design of new drugs from "first principles", screening will continue to play a major role in the discovery of new leads for anticancer drugs, just as it does in the discovery of chemotherapeutic agents for other diseases.

# ABBREVIATIONS

AZQ	- Aziridinybenzoquinone analog
CBDCA	- Cisplatin analog
cis-Pt	- Cisplatin
DACH	- Cisplatin analog
DN2A	- First Decision Network point in the selection of clinical candidates - also, a defined, high level of tumor panel activity
DN2B	- Decision Network point which authorizes toxicology studies
DTIC	- Dacarbazine
DTP	- Developmental Therapeutics Program
ICI	- Imperial Chemicals Industry
ICN	- International Chemicals and Nuclear Corp.
ICRF	- Imperial Cancer Research Foundation
IMC	- Institute of Microbial Chemistry, Tokyo (Umezawa)
INDA	- Investigational New Drug Application
MDA	- M.D. Anderson Hospital and Tumor Institute
MRI	- Midwest Research Institute
MSKCC	- Memorial Sloan Kettering Cancer Center
NDA	- New Drug Application
PCNU	- Nitrosourea analog
PMM	- Pentamethylmetamine
So.R.I.	- Southern Research Institute
Stanford R.I.	- Stanford Research Institute
SUNY	- State University of New York (Buffalo)
THC	- Tetrahydrocannabinol
Trimethyl TMM	- Trimethyl trimethylmelamine
USC	- University of Southern California
USDA	- U.S. Department of Agriculture







National Cancer Institute